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(54) Title: ARYLOXY AND ARYLALKYLEOXY SUBSTITUTED THIAZOLOQUINOLINES AND THIAZOLONAPHTHYRIDINES

(57) Abstract: Thiazoloquinoline and thiazolonaphthyridine compounds having an aryloxy or arylalkyleneoxy substituent at the 6-, 7-, 8-, or 9-position, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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ARYLOXY AND ARYLALKYLENEOXY SUBSTITUTED THIAZOLOQUINOLINES AND THIAZOLONAPHTHYRIDINES

5

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/581297, filed June 18, 2004, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

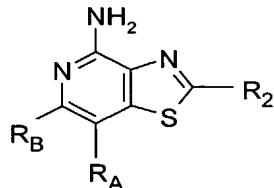
10 In the 1950's the *1H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-*1H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted *1H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-*1H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

15 Certain *1H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted *1H*-imidazo[4,5-*c*] pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and 20 tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

25 But despite important progress in the effort to find immunomodulating compounds, there is still a critical scientific and medical need for additional compounds that have an ability to modulate aspects of the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY OF THE INVENTION

The present invention provides a new class of compounds that are useful in modulating cytokine biosynthesis in animals. In one aspect, the present invention provides compounds of the Formula I:



5

wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R_3 group, or substituted by one R_3 group and one R group; and

10

R_3 is selected from the group consisting of:

- O-Z-Ar,
- O-Z-Ar'-Y-R₄,
- O-Z-Ar'-X-Y-R₄,
- 15 -O-Z-Ar'-R₅, and
- O-Z-Ar'-X-R₅;

15

wherein R , R_2 , Z , Ar , Ar' , X , Y , R_4 , and R_5 are as defined below; and pharmaceutically acceptable salts thereof.

20

The compounds of Formula I are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested, for example, using the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μ M and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μ M and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate

cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

5 In another aspect, the present invention provides pharmaceutical compositions containing an effective amount of a compound of Formula I, and methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal an effective amount of a compound of Formula I and/or a pharmaceutically acceptable salt thereof.

10 In another aspect, the invention provides methods of synthesizing the compounds of Formula I and intermediates useful in the synthesis of these compounds.

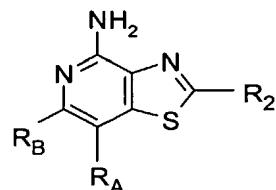
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

15 The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In 20 each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive or exhaustive list.

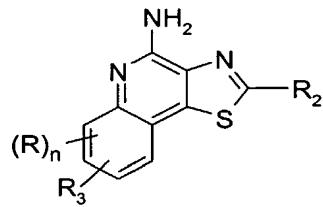
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

25 The present invention provides compounds of the following Formula (I):

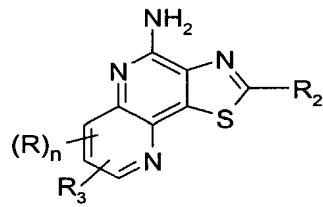


I

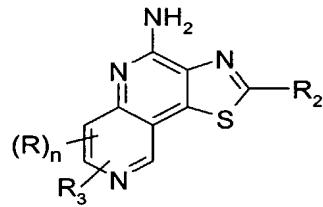
as well as more specific compounds of the following Formulas (II, III, IV, V, VI, IIIa, IVa, VIa, and VII):



II

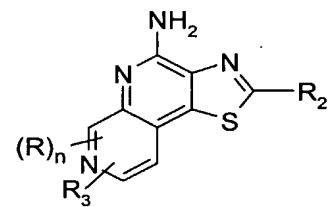


III



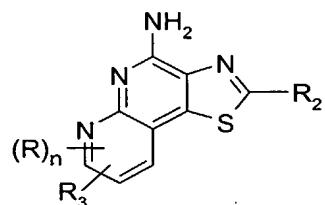
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IV

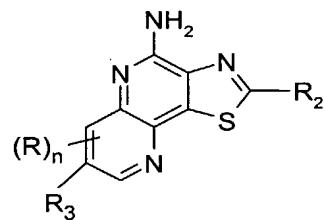


V

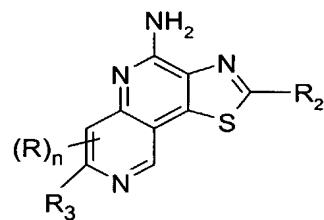
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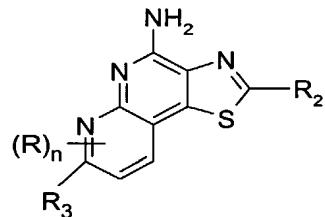
VI



IIIa

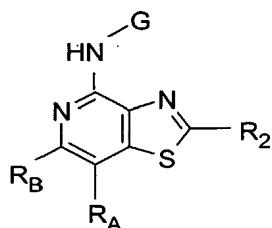


IVa



10

VIa.



VII

wherein R_A , R_B , R , R_2 , R_3 , G , and n are as defined below, and pharmaceutically acceptable salts thereof.

For any of the compounds presented herein, each one of the following variables (e.g., A , X , Y , Z , R_A , R_B , R , R_2 , R_3 , Q , G , n , and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

10 In some embodiments, R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R_3 group, or substituted by one R_3 group and one R group. In some embodiments, R_3 is attached at the 7-position.

15 In some embodiments, R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl.

In some embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, hydroxyalkylenyl, haloalkylenyl, alkenyl, alkyl-O-alkylenyl, alkyl-O-alkenylenyl, alkenyl-O-alkylenyl, alkenyl-O-alkenylenyl, $N(R_8)_2$ -alkylenyl, N_3 -alkylenyl, $N(R_8)_2$ -C(O)-O-alkylenyl, heterocyclyl, heterocyclyl-O-alkylenyl, heterocyclyl-O-alkenylenyl, aryl, aryl-O-alkylenyl, aryl-O-alkenylenyl, heteroaryl, heteroaryl-O-alkylenyl, and heteroaryl-O-alkenylenyl.

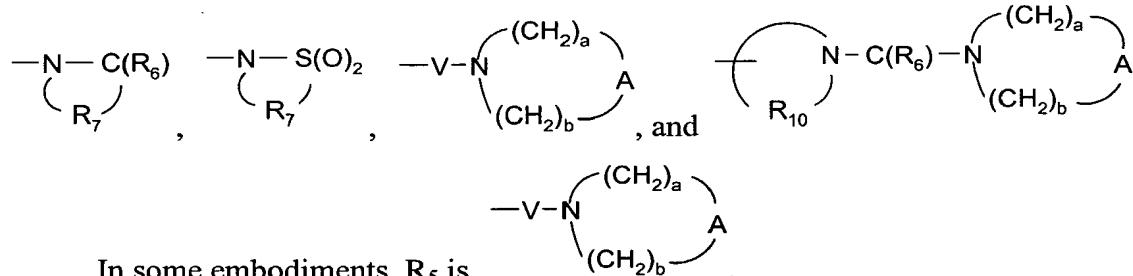
20 In some embodiments, R_2 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-8} alkyl-O- C_{1-8} alkylenyl. In some embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O- C_{1-4} alkylenyl. In some embodiments, R_2 is methyl, ethyl, n-propyl, n-butyl, 2-methoxyethyl, methoxymethyl, or ethoxymethyl.

25 In some embodiments, R_3 is selected from the group consisting of -O-Z-Ar, -O-Z-Ar'-Y-R₄, -O-Z-Ar'-X-Y-R₄, -O-Z-Ar'-R₅, and -O-Z-Ar'-X-R₅. In some embodiments, R_3 is -O-Z-Ar'-Y-R₄, -O-Z-Ar-X-Y-R₄, or -O-Z-Ar'-R₅. In some embodiments, R_3 is -O-Z-Ar'-Y-R₄. In some embodiments, R_3 is -O-Z-Ar.

30 In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl

wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. In some embodiments, R₄ is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl. In some embodiments, R₄ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl. In some embodiments, R₄ is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl. In some embodiments, R₄ is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl.

15 In some embodiments, R₅ is selected from the group consisting of



In some embodiments, R₅ is

In some embodiments, R₆ is selected from the group consisting of =O and =S.

In some embodiments, R₇ is C₂₋₇ alkylene.

20 In some embodiments, R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl. In some embodiments, R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl.

In some embodiments, R₉ is selected from the group consisting of hydrogen and alkyl.

25 In some embodiments, R₁₀ is C₃₋₈ alkylene.

In some embodiments, Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy,

methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino.

5 In some embodiments, particularly when R_3 is $-O-Z-Ar$, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, 1,2,3-triazolyl, indolyl, benzothiazolyl, and oxazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, 10 dialkylamino, trifluoromethoxy, aryl, and hydroxyalkyl. In some embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, and 15 trifluoromethoxy. In some embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, and trifluoromethoxy. In some embodiments, Ar is phenyl 20 substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, and trifluoromethoxy. In some embodiments, Ar is phenyl substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, and trifluoromethoxy.

25 In some embodiments, Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, 30 heterocyclyl, heterocyclalkylenyl, amino, alkylamino, and dialkylamino. In some embodiments, Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene. In some embodiments, Ar' is phenylene.

In some embodiments, A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-.

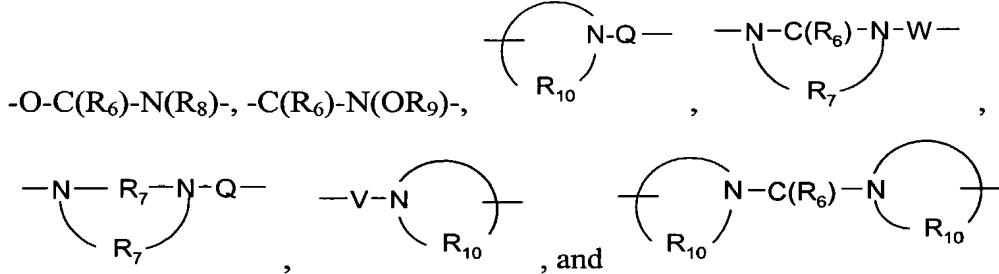
In some embodiments, Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-. In some embodiments, Q is selected from the group consisting of a bond, -C(O)-, -S(O)₂-, and -C(R₆)-N(R₈)-.

In some embodiments, V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-.

In some embodiments, W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-.

In some embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclylene or by one or more -O- groups. In some embodiments, X is C₁₋₄ alkylene.

In some embodiments, Y is selected from the group consisting of -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-,



In some embodiments, Y is selected from the group consisting of -S(O)₀₋₂-, -C(O)-, -C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, and -C(R₆)-N(OR₉)-. In some embodiments, Y is -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(O)-, -N(R₈)-C(O)-, -N(R₈)-S(O)₂-, and -N(R₈)-C(R₆)-N(R₈)-. In some embodiments, Y is -S(O)₂-, -C(O)-, -N(R₈)-C(O)-, -N(R₈)-S(O)₂-, and -N(R₈)-C(R₆)-N(R₈)-. In some embodiments, Y is -S(O)₂-, -C(O)-N(R₈)-, or -N(R₈)-Q-. In some embodiments, Y is -N(R₈)-C(R₆)-. In some embodiments, Y is -N(R₈)-S(O)₂-. In some embodiments, Y is -N(R₈)-C(R₆)-N(R₈)-.

In some embodiments, Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-. In some embodiments, Z is a bond, alkylene, or alkylene interrupted with one -O-. In some embodiments, Z is -C₁₋₃ alkylene-. In some embodiments, Z is -CH₂-.

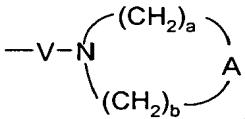
5 In some embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

In some embodiments, n is 0 or 1. In some embodiments, n is 0.

For certain embodiments of the compounds of Formulas (I) through (VI), the 10 -NH₂ group can be replaced by an -NH-G group, as shown in the compound of Formula (VII), to form prodrugs. In such embodiments, G is selected from the group consisting of: -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, and -CH(CH₃)Y₁. In some of these embodiments G is -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, 15 or -C(O)-O-R'. Preferably, R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylene, heteroarylC₁₋₄ alkylene, haloC₁₋₄ alkylene, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, 20 -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂. R" can also be hydrogen. Preferably, α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y' is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl. Preferably, Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkylene, aminoC₁₋₄ alkylene, mono-N-C₁₋₆ 25 alkylaminoC₁₋₄ alkylene, and di-N,N-C₁₋₆ alkylaminoC₁₋₄ alkylene. Preferably, Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl.

In some embodiments, R₃ is -O-Z-Ar'-Y-R₄, -O-Z-Ar-X-Y-R₄, or -O-Z-Ar'-R₅. In some embodiments, R₃ is -O-Z-Ar'-Y-R₄. In such embodiments of R₃, Ar' is phenylene, 30 naphthylene, pyridylene, pyrrolylene, thienylene, or furylene; Y is selected from the group consisting of -S(O)₀₋₂-, -C(O)-, -C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, and

-C(R₆)-N(OR₉)-; X is C₁₋₄ alkylene; R₄ is selected from the group consisting of hydrogen,

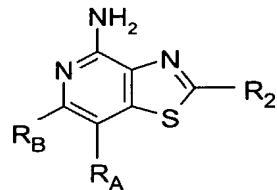
alkyl, aryl, heteroaryl, and heterocyclyl; and R₅ is . In such embodiments, preferably, Q is selected from the group consisting of a bond, -C(O)-, -S(O)₂-, and -C(R₆)-N(R₈)-; and R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl.

5 Alternatively, in such embodiments of R₃, particularly when R₃ is -O-Z-Ar'-Y-R₄, preferably Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene (more preferably, phenylene); Y is selected from the group consisting of -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(O)-, -N(R₈)-C(O)-, -N(R₈)-S(O)₂-, and -N(R₈)-C(R₆)-N(R₈)-; and R₄ is selected from the group consisting of alkyl, aryl, heteroaryl, heteroarylalkylenyl, and heterocyclyl. In such embodiments, preferably, R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl.

10 In some embodiments of R₃, Y is -N(R₈)-C(R₆)-; R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In some embodiments of R₃, Y is -N(R₈)-S(O)₂-, R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In some embodiments of R₃, Y is -N(R₈)-C(R₆)-N(R₈)-; R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl.

15 In some embodiments of R₃, Y is -S(O)₂-, -C(O)-N(R₈)-, or -N(R₈)-Q-; R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl; and R₄ is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl.

20 In one aspect, the present invention provides thiazoloquinoline and thiazolonaphthyridine compounds of the following formula (I):



I

wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R₃ group, or substituted by one R₃ group and one R group;

5 R₂ is selected from the group consisting of:

hydrogen,
alkyl,
hydroxyalkylenyl,
haloalkylenyl,
10 alkenyl,
alkyl-O-alkylenyl,
alkyl-O-alkenyl-enyl,
alkenyl-O-alkylenyl,
alkenyl-O-alkenyl-enyl,

15 N(R₈)₂-alkylenyl,
N₃-alkylenyl,
N(R₈)₂-C(O)-O-alkylenyl,
heterocyclyl,
heterocyclyl-O-alkylenyl,

20 heterocyclyl-O-alkenyl-enyl,
aryl,
aryl-O-alkylenyl,
aryl-O-alkenyl-enyl,
heteroaryl,
25 heteroaryl-O-alkylenyl, and
heteroaryl-O-alkenyl-enyl;

R₃ is selected from the group consisting of:

-O-Z-Ar,
-O-Z-Ar'-Y-R₄,
30 -O-Z-Ar'-X-Y-R₄,
-O-Z-Ar'-R₅, and
-O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-;

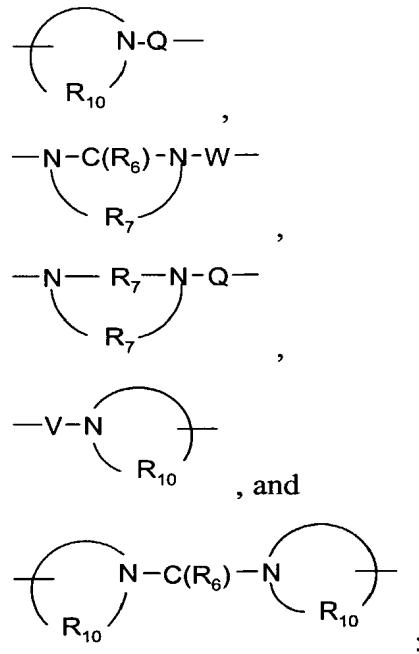
5 Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylene, amino, alkylamino, and dialkylamino;

10 Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylene, amino, alkylamino, and dialkylamino;

15 X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclylene or by one or more -O- groups.

20 Y is selected from the group consisting of:

- S(O)₀₋₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-O-,
- 25 -O-C(R₆)-,
- O-C(O)-O-,
- N(R₈)-Q-,
- C(R₆)-N(R₈)-,
- O-C(R₆)-N(R₈)-,
- 30 -C(R₆)-N(OR₉)-,

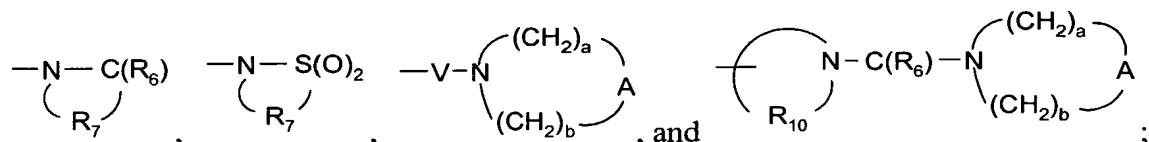


5

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

15

R₅ is selected from the group consisting of:



20

R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;
R₁₀ is C₃₋₈ alkylene;
A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

5 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

10 W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-, a and b are independently integers from 1 to 6 with the proviso that a + b is \leq 7; and

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

15 In some embodiments, compounds or salts of Formula I induce the biosynthesis of one or more cytokines.

In some embodiments of Formula I, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-.

20 In some embodiments of Formula I, R₃ is -O-Z-Ar. In certain embodiments, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-.

In some embodiments of Formula I, R₃ is -O-Z-Ar'-Y-R₄, -O-Z-Ar'-X-Y-R₄, or -O-Z-Ar-R₅. In certain embodiments, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-.

25 In some embodiments of Formula I, R₃ is -O-Z-Ar'-Y-R₄. In certain embodiments, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Y is -S(O)₂-, -C(O)-N(R₈)-, or -N(R₈)-Q-; R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and

30 alkoxylalkylenyl; and R₄ is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl.

heteroaryl-O-alkylenyl, and

heteroaryl-O-alkenylenyl;

R₃ is selected from the group consisting of:

-O-Z-Ar,

5 -O-Z-Ar'-Y-R₄,

-O-Z-Ar'-X-Y-R₄,

-O-Z-Ar'-R₅, and

-O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and

10 alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,

15 haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents

20 independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclene or by one or more -O- groups.

Y is selected from the group consisting of:

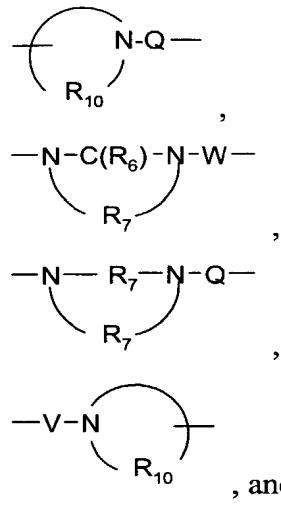
-S(O)₀₋₂-,

30 -S(O)₂-N(R₈)-,

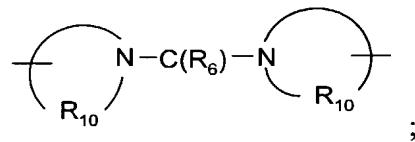
-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,
- $O-C(O)-O-$,
-N(R₈)-Q-,
-C(R₆)-N(R₈)-,
5 -O-C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-,

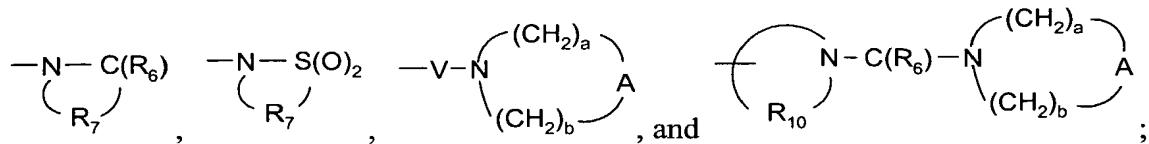


10 , and



R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

5 R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

10 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,

15 W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-,

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7 ;

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

20 or a pharmaceutically acceptable salt thereof.

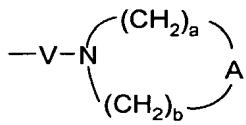
In some embodiments of Formula II, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂-.

25 In some embodiments of Formula II, R₃ is -O-Z-Ar. In certain embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, 1,2,3-triazolyl, indolyl, benzothiazolyl, and oxazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethoxy, aryl, and hydroxyalkyl. In certain

embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, or trifluoromethoxy. In certain embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, and trifluoromethoxy.

10 In certain embodiments, Ar is phenyl substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, or trifluoromethoxy. In certain embodiments, phenyl substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, 15 dialkylamino, and trifluoromethoxy. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂-.

20 In some embodiments of Formula II, R₃ is -O-Z-Ar'-Y-R₄, -O-Z-Ar-X-Y-R₄, or -O-Z-Ar'-R₅. In certain embodiments, Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene; Y is selected from the group consisting of -S(O)₀₋₂-, -C(O)-, -C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, and -C(R₆)-N(OR₉)-; wherein Q is selected from the group consisting of a bond, -C(O)-, -S(O)₂-, and -C(R₆)-N(R₈)-; and R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl; X is C₁₋₄ alkylene; R₄ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; and R₅ is



25 . In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂-.

In certain embodiments, R₃ is -O-Z-Ar'-Y-R₄.

In some embodiments of Formula II, R₃ is -O-Z-Ar'-Y-R₄. In certain embodiments, Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene; Y is selected from the group consisting of -S(O)₀₋₂-, -C(O)-, -N(R₈)-C(O)-,

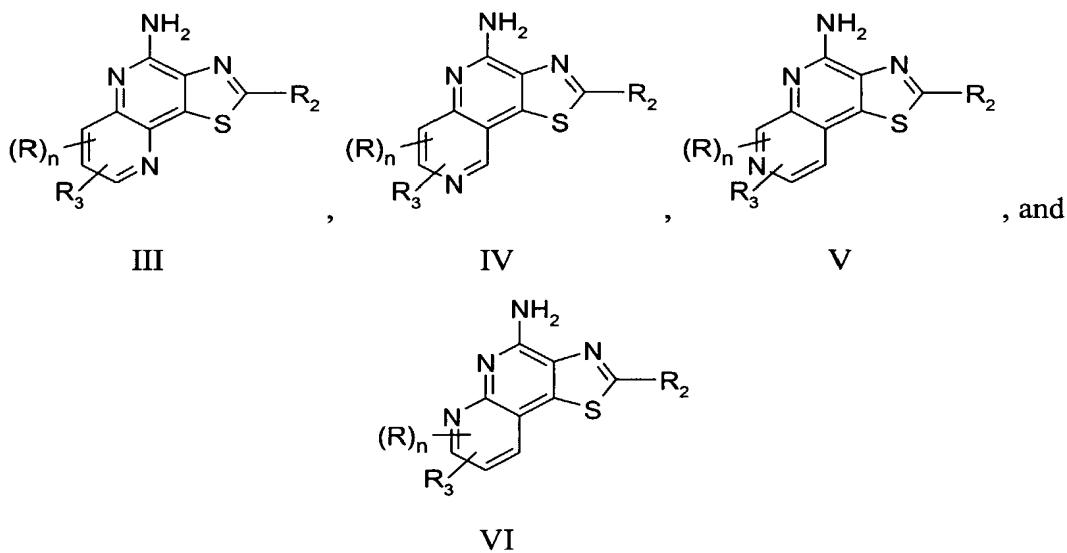
-N(R₈)-S(O)₂-, and -N(R₈)-C(R₆)-N(R₈)-, wherein R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl; and R₄ is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl. In certain embodiments, Y is -N(R₈)-C(R₆)-; R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In certain other embodiments, Y is -N(R₈)-S(O)₂-, R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In certain other embodiments, Y is -N(R₈)-C(R₆)-N(R₈)-; R₄ is alkyl, aryl, heteroaryl, or heterocyclyl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl.

In some embodiments of Formula II and any one of the above embodiments of Formula II, R₂ is selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ alkyl-O-C₁₋₈ alkylenyl. In certain embodiments, R₂ is hydrogen, C₁₋₄ alkyl or C₁₋₄ alkyl-O-C₁₋₄ alkylenyl. In certain more specific embodiments, R₂ is methyl, ethyl, n-propyl, n-butyl, 2-methoxyethyl, methoxymethyl, or ethoxymethyl.

In some embodiments of Formula II and any one of the above embodiments of Formula II, R₃ is attached at the 7-position.

In some embodiments of Formula II and any one of the above embodiments of Formula II, n is 0.

The present invention also provides thiazolonaphthyridine compounds of the following formulas (III, IV, V, and VI):



wherein:

R₂ is selected from the group consisting of:

hydrogen,
alkyl,
5 hydroxyalkylenyl,
haloalkylenyl,
alkenyl,
alkyl-O-alkylenyl,
alkyl-O-alkenylenyl,
10 alkenyl-O-alkylenyl,
alkenyl-O-alkenylenyl,
N(R₈)₂-alkylenyl,
N₃-alkylenyl,
N(R₈)₂-C(O)-O-alkylenyl,
15 heterocyclyl,
heterocyclyl-O-alkylenyl,
heterocyclyl-O-alkenylenyl,
aryl,
aryl-O-alkylenyl,
20 aryl-O-alkenylenyl,
heteroaryl,
heteroaryl-O-alkylenyl, and
heteroaryl-O-alkenylenyl;

R₃ is selected from the group consisting of:

25 -O-Z-Ar,
-O-Z-Ar'-Y-R₄,
-O-Z-Ar'-X-Y-R₄,
-O-Z-Ar'-R₅, and
-O-Z-Ar'-X-R₅;

30 Z is selected from the group consisting of a bond, alkylene, alkenylene, and
alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with
-O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, 5 aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, 10 haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

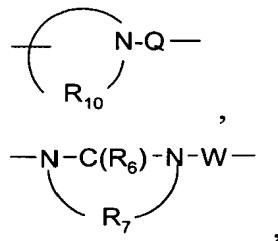
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and 15 alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclene or by one or more -O- groups.

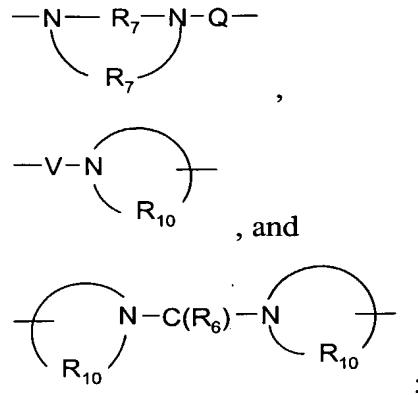
Y is selected from the group consisting of:

-S(O)₀₋₂-,
-S(O)₂-N(R₈)-,

20 -C(R₆)-,
-C(R₆)-O-,
-O-C(R₆)-,
-O-C(O)-O-,
-N(R₈)-Q-,

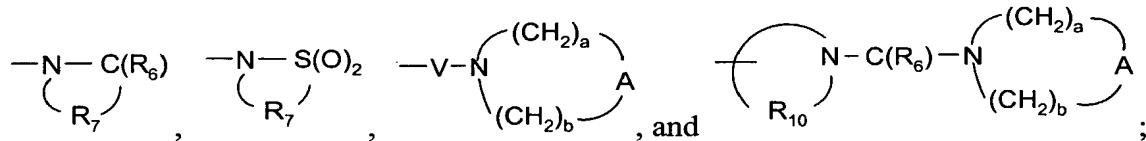
25 -C(R₆)-N(R₈)-,
-O-C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-,





R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, 5 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected 10 from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

15 R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

20 R₈ is selected from the group consisting of hydrogen, alkyl, aryloxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

25 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-,

-S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

5 a and b are independently integers from 1 to 6 with the proviso that a + b is \leq 7;

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

10

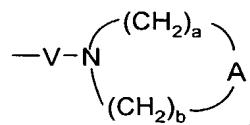
In some embodiments of Formulas III, IV, V, and VI, Z is a bond, alkylene, or alkylene interrupted with one -O-. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂-.

15

In some embodiments of Formulas III, IV, V, and VI, R₃ is -O-Z-Ar. In certain embodiments, Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, or trifluoromethoxy. In certain embodiments, Ar is phenyl substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethyl, or trifluoromethoxy. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂-.

20

In some embodiments of Formulas III, IV, V, and VI, R₃ is -O-Z-Ar'-Y-R₄, -O-Z-Ar-X-Y-R₄, or -O-Z-Ar'-R₅. In certain embodiments, Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene; Y is selected from the group consisting of -S(O)₂-, -C(O)-, -C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, and -C(R₆)-N(OR₉)-; wherein Q is selected from the group consisting of a bond, -C(O)-, -S(O)₂-, and -C(R₆)-N(R₈)-; and R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and alkoxyalkylenyl; X is C₁₋₄ alkylene; R₄ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; and R₅ is



. In certain embodiments, Z is -C₁₋₃ alkylene-. In certain embodiments, Z is -CH₂- . In certain embodiments, R₃ is -O-Z-Ar'-Y-R₄.

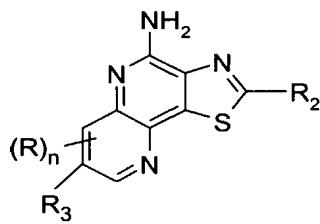
In some embodiments of Formulas III, IV, V, and VI, R₃ is -O-Z-Ar'-Y-R₄. In certain embodiments, Y is -N(R₈)-C(R₆)-; R₄ is alkyl, aryl, heteroaryl, or heterocycl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In certain other embodiments, Y is -N(R₈)-S(O)₂-; R₄ is alkyl, aryl, heteroaryl, or heterocycl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl. In certain other embodiments, Y is -N(R₈)-C(R₆)-N(R₈)-; R₄ is alkyl, aryl, heteroaryl, or heterocycl; and R₈ is hydrogen, C₁₋₄ alkyl, or alkoxyalkylenyl.

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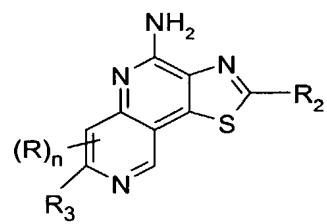
In some embodiments of Formulas III, IV, V, and VI and any one of the above embodiments of Formulas III, IV, V, and VI, R₂ is selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ alkyl-O-C₁₋₈ alkylene. In certain embodiments, R₂ is hydrogen, C₁₋₄ alkyl or C₁₋₄ alkyl-O-C₁₋₄ alkylene. In certain more specific embodiments, R₂ is methyl, ethyl, n-propyl, n-butyl, 2-methoxyethyl, methoxymethyl, or ethoxymethyl.

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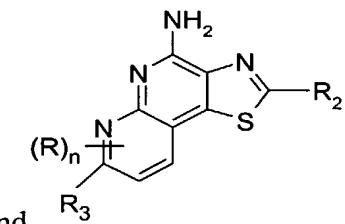
In some embodiments of Formulas III, IV, and VI and any one of the above embodiments described above for Formulas III, IV, and VI, R₃ is attached at the 7-position. That is, the thiazolonaphthyridines selected from Formulas III, IV, V, and VI are the compounds of the formulas (IIIa, IVa, and VIa):



IIIa



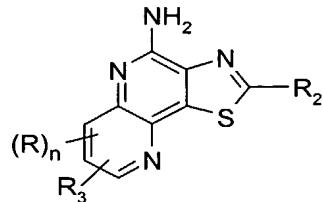
IVa



VIa.

20

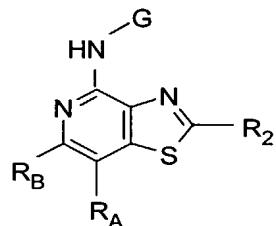
In some embodiments, the thiazolonaphthyridines selected from Formulas III, IV, V, and VI or any one of the above embodiments described above for Formulas III, IV, V, and VI are the compounds of the formula (III):



III.

5 In some embodiments of Formulas III, IV, V, and VI or any one of the above
embodiments of Formulas III, IV, V, and VI, n is 0.

In another aspect of the invention, there is provided a compound (which is a prodrug) of the formula (VII):



VII

10 wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R₃ group, or substituted by one R₃ group and one R group;

15 R₂ is selected from the group consisting of:

- hydrogen,
- alkyl,
- hydroxyalkylenyl,
- haloalkylenyl,
- 20 alkenyl,
- alkyl-O-alkylenyl,
- alkyl-O-alkenylenyl,
- alkenyl-O-alkylenyl,
- alkenyl-O-alkenylenyl,

N(R₈)₂-alkylenyl,
N₃-alkylenyl,
N(R₈)₂-C(O)-O-alkylenyl,
heterocyclyl,
5 heterocyclyl-O-alkylenyl,
heterocyclyl-O-alkenylenyl,
aryl,
aryl-O-alkylenyl,
aryl-O-alkenylenyl,
10 heteroaryl,
heteroaryl-O-alkylenyl, and
heteroaryl-O-alkenylenyl;

R₃ is selected from the group consisting of:

-O-Z-Ar,
15 -O-Z-Ar'-Y-R₄,
-O-Z-Ar'-X-Y-R₄,
-O-Z-Ar'-R₅, and
-O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and
20 alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with
-O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can
be unsubstituted or can be substituted by one or more substituents independently selected
from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,
25 haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,
aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy,
heterocyclyl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of
which can be unsubstituted or can be substituted by one or more substituents
30 independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl,
haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,

aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylenyl, amino, alkylamino, and dialkylamino;

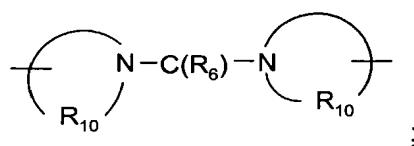
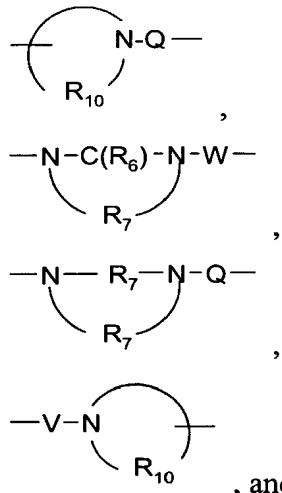
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclene or by one or more -O- groups.

Y is selected from the group consisting of:

-S(O)₀₋₂-,
-S(O)₂-N(R₈)-,

10 -C(R₆)-,
-C(R₆)-O-,
-O-C(R₆)-,
-O-C(O)-O-,
-N(R₈)-Q-,

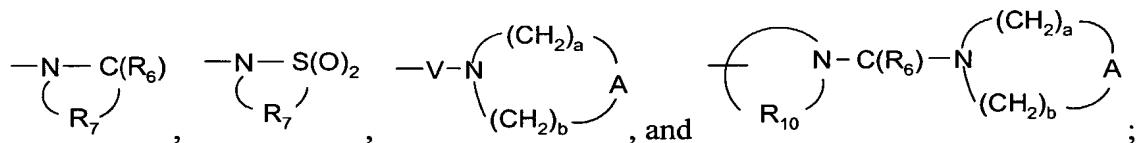
15 -C(R₆)-N(R₈)-,
-O-C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-,



R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

10 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

15 R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

20 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-,

25 a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

G is selected from the group consisting of:

-C(O)-R',

α -aminoacyl,

30

5 α -aminoacyl- α -aminoacyl,
-C(O)-O-R',
-C(O)-N(R")R',
-C(=NY')-R',
-CH(OH)-C(O)-OY',
-CH(OC₁₋₄ alkyl)Y₀,
-CH₂Y₁, and
-CH(CH₃)Y₁;

R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl,
10 C₃₋₇ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or
more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano,
carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkyl enyl,
heteroarylC₁₋₄ alkyl enyl, haloC₁₋₄ alkyl enyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃,
-C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also
15 be hydrogen;

α -aminoacyl is an acyl group derived from an amino acid selected from the group
consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl;

20 Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkyl enyl,
aminoC₁₋₄ alkyl enyl, mono-*N*-C₁₋₆ alkylaminoC₁₋₄ alkyl enyl, and
di-*N,N*-C₁₋₆ alkylaminoC₁₋₄ alkyl enyl;

Y₁ is selected from the group consisting of mono-*N*-C₁₋₆ alkylamino,
di-*N,N*-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and
4-C₁₋₄ alkylpiperazin-1-yl;

25 or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are
inclusive of both straight chain and branched chain groups and of cyclic groups, e.g.,
cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to
30 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl
groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a
total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4

carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

5 Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms "alkylenyl," "alkenylene," and "alkynylene" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

10 The term "haloalkyl" is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

15 The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

20 The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and/or N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

25 The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl,

5 isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,4-oxazepanyl, 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

10 The term "heterocyclyl" includes bicyclic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

15 The terms "arylene," "heteroarylene," and "heterocyclene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

20 When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether specifically stated or not. For example, for the formula N(R₈)₂-alkylenyl, each R₈ group is independently selected.

25 The invention is inclusive of the compounds described herein and salts thereof in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

30 The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms

described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American 5 Pharmaceutical Association and Pergamon Press, 1987.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that 10 include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic 15 Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritzky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, 20 Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific 25 starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using 30 conventional methods well known to those skilled in the art.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such

techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

5 Compounds of the invention can be prepared according to Reaction Scheme I where R, R₂, and n are as defined above and R_{3a} is -Z-Ar or -Z-Ar'-Y-R₄, where Z, Ar, Ar', Y, and R₄ are as defined above. In step (1) of Reaction Scheme I, a benzyloxyaniline of Formula XV is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide a dione of

10 Formula XVI. The reaction is conveniently carried out by adding a solution of a benzyloxyaniline of Formula XV to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C.

15 In step (2) of Reaction Scheme I, a dione of Formula XVI undergoes thermolysis and cyclization to provide a benzyloxyquinolin-4-ol of Formula XVII. The reaction is conveniently carried out in a heat transfer fluid such as DOWTHERM A at a temperature between 200 and 250 °C.

20 In step (3) of Reaction Scheme I, the benzyloxyquinolin-4-ol of Formula XVII is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula XVIII. The reaction is conveniently carried out by adding nitric acid to the benzyloxyquinolin-4-ol of Formula XVII in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C.

25 In step (4) of Reaction Scheme I, a benzyloxy-3-nitroquinolin-4-ol of Formula XVIII is reduced to provide a 3-amino-benzyloxyquinolin-4-ol of Formula XIX. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as *N,N*-dimethylformamide. The reaction can be carried out at ambient temperature.

30 In step (5) of Reaction Scheme I, a 3-amino-benzyloxyquinolin-4-ol of Formula XIX is reacted with a carboxylic acid or an equivalent thereof to provide a compound of Formula XX. Suitable equivalents to carboxylic acid include acid anhydrides and acid chlorides. The reaction is conveniently carried out by adding the acid chloride to a solution of a 3-amino-benzyloxyquinolin-4-ol of Formula XIX in a suitable solvent such

as dichloromethane or acetonitrile in the presence of a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine to afford an amide. The reaction can be carried out at or below ambient temperature.

5 In step (6) of Reaction Scheme I, an amide of Formula XX is reacted with phosphorus pentasulfide to provide a benzyloxy-thiazolo[4,5-*c*]quinoline of Formula XXI. The reaction can be carried out by adding phosphorus pentasulfide to a solution or suspension of a compound of Formula XX in a suitable solvent such as pyridine and heating the resulting mixture.

10 In step (7) of Reaction Scheme I, a benzyloxy-thiazolo[4,5-*c*]quinoline of Formula XXI is oxidized to provide a benzyloxy-thiazolo[4,5-*c*]quinoline-5*N*-oxide of Formula XXII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXI in a solvent such dichloromethane or chloroform. The reaction can be carried out at ambient temperature.

15 In step (8) of Reaction Scheme I, a benzyloxy-thiazolo[4,5-*c*]quinoline-5*N*-oxide of Formula XXII is aminated to provide a benzyloxy-thiazolo[4,5-*c*]quinolin-4-amine of Formula XXIII. Step (8) can be carried out by the activation of an *N*-oxide of Formula XXII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl 20 chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide followed by *p*-toluenesulfonyl chloride to a solution of the *N*-oxide of Formula XXII in a 25 suitable solvent such as 1,2-dichloroethane at elevated temperature. The reaction may be carried out by adding ammonium hydroxide and *p*-toluenesulfonyl chloride to the reaction mixture from step (7) without isolating the *N*-oxide of Formula XXII

30 Alternatively step (8) can be carried out by the reaction of a benzyloxy-thiazolo[4,5-*c*]quinoline-5*N*-oxide of Formula XXII with trichloroacetyl isocyanate followed by hydrolysis of the resulting intermediate to provide a benzyloxy-thiazolo[4,5-*c*]quinoline-4-amine of Formula XXIII. The reaction is conveniently carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution of the *N*-oxide of Formula XXII

in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide or ammonium hydroxide at ambient temperature.

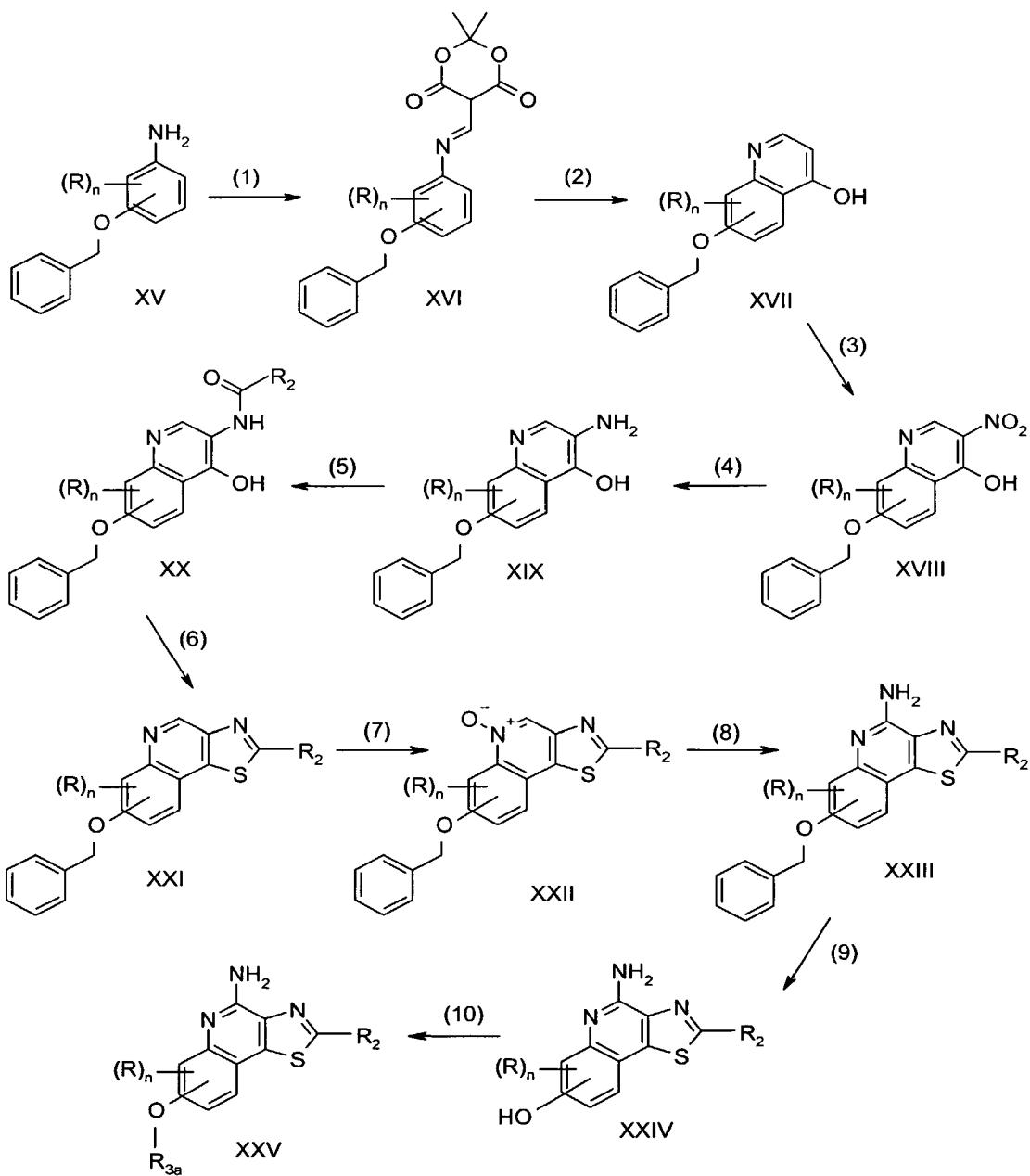
5 In step (9) of Reaction Scheme I, the benzyl group of a benzyloxy-thiazolo[4,5-*c*]quinoline-4-amine of Formula XXIII is cleaved to provide a thiazolo[4,5-*c*]quinolinol of Formula XXIV. The cleavage is conveniently carried out with an acid such as hydrogen bromide in a suitable solvent such as acetic acid at elevated temperature.

10 Alternatively, the cleavage may be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol.

15 In step (10) of Reaction Scheme I, a thiazolo[4,5-*c*]quinolinol of Formula XXIV is converted to an ether-substituted thiazolo[4,5-*c*]quinoline-4-amine of Formula XXV using a Williamson-type ether synthesis. The reaction is effected by treating a thiazolo[4,5-*c*]quinolinol of Formula XXIV with an alkyl or aryl halide of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄ in the presence of a base. Numerous reagents of Formulae Halide-Z-Ar and Halide-Z-Ar'-Y-R₄ are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other reagents of Formulae Halide-Z-Ar and 20 Halide-Z-Ar'-Y-R₄ can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining a reagent of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄ with a thiazolo[4,5-*c*]quinolinol of Formula XXIV in a solvent such as *N,N*-dimethylformamide (DMF) in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction 25 can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C, depending on the reactivity of the reagent of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

30 Alternatively, step (10) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide of a thiazolo[4,5-*c*]quinolinol of Formula XXIV reacts with an aryl halide in the presence of copper salts, to provide compounds of Formula XXV, where R_{3a} is -Z-Ar or -Z-Ar'-Y-R₄, and Z is a bond.

Reaction Scheme I



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Compounds of the invention can also be prepared according to Reaction Scheme II, where R, R₂, and n are as defined above and R_{3a} is -Z-Ar or -Z-Ar'-Y-R₄, where Z, Ar, Ar', Y, and R₄ are as defined above. In step (1) of Reaction Scheme II, the benzyl group of a benzyloxy-thiazolo [4,5-c]quinoline of Formula XXI is cleaved to provide a

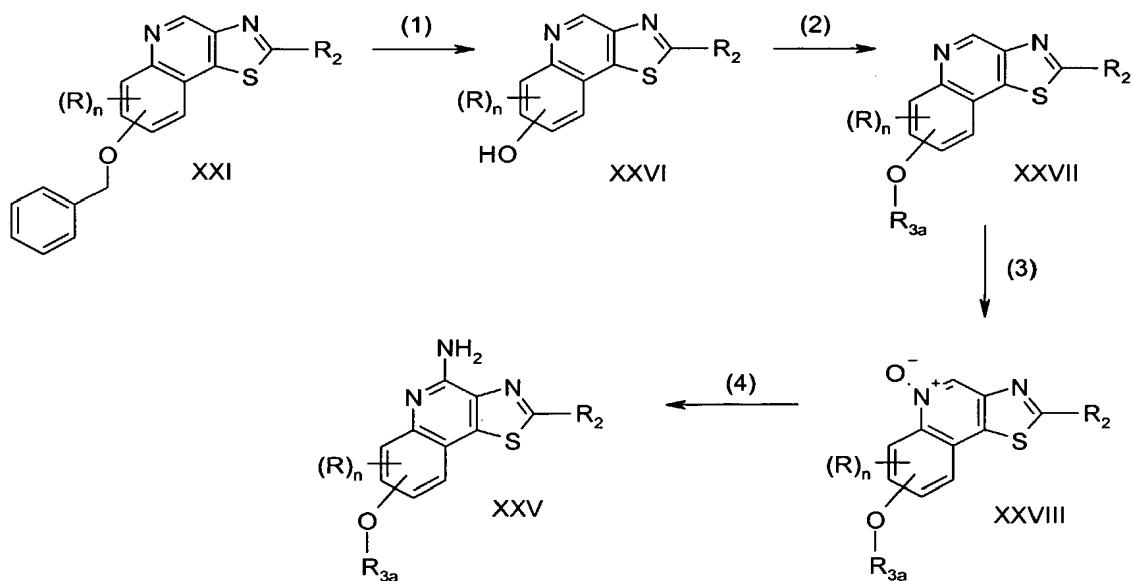
thiazolo[4,5-*c*]quinolinol of Formula XXVI. The reaction can be carried out as described in step (9) of Reaction Scheme I.

In step (2) of Reaction Scheme II, a thiazolo[4,5-*c*]quinolinol of Formula XXVI is treated with an alkyl or aryl halide of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄ to afford an ether-substituted thiazolo[4,5-*c*]quinoline of Formula XXVII. The reaction can be carried out as described in step (10) of Reaction Scheme I.

In steps 3 and 4 of Reaction Scheme II, an ether-substituted thiazolo[4,5-*c*]quinoline of Formula XXVII is oxidized to afford a thiazolo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVIII, which is aminated to provide a thiazolo[4,5-*c*]quinolin-4-amine of Formula XXV. Steps (3) and (4) can be carried out as described in steps (7) and (8), respectively, of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Further synthetic elaboration of ether-substituted thiazolo[4,5-*c*]quinolin-4-amines of Formula XXV, prepared in Reaction Scheme I or II, is possible. For example, a nitro substituent on the aryl or heteroaryl group on a compound of Formula II, where R_{3a} is -Z-Ar, can be reduced to an amino group using conventional methods. The reduction can be carried out using the methods described in step (4) of Reaction Scheme I.

Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III where R, R₂, and n are as defined above and R_{3a} is -Z-Ar or -Z-Ar'-Y-R₄, where Z, Ar, Ar', Y, and R₄ are as defined above. In step (1) of Reaction Scheme III, a 5 benzyloxypyridine of Formula XXX is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide a dione of Formula XXXI. The reaction is conveniently carried out by adding a solution of a benzyloxypyridine of Formula XXX to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. Benzyloxypyridines of Formula XXX can be prepared using conventional synthetic 10 methods; see for example, Holladay et al., *Biorg. Med. Chem. Lett.*, (8), 1998, 2797-2802.

In step (2) of Reaction Scheme III, a dione of Formula XXXI undergoes thermolysis and cyclization to provide a benzyloxy[1,5]naphthyridin-4-ol of Formula XXXII. The reaction is conveniently carried out in a heat transfer fluid such as DOWTHERM A at a temperature between 200 and 250 °C.

15 In step (3) of Reaction Scheme III, the benzyloxy[1,5]naphthyridin-4-ol of Formula XXXII is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula XXXIII. The reaction is conveniently carried out by adding nitric acid to the benzyloxy[1,5]naphthyridin-4-ol of Formula XXXII in a suitable solvent such as propionic acid and heating the mixture at an 20 elevated temperature such as 125 °C.

25 In step (4) of Reaction Scheme III, a benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula XXXIII is reduced to provide a 3-amino-benzyloxy[1,5]naphthyridin-4-ol of Formula XXXIV. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as dimethylformamide. The reaction can be carried out at ambient temperature.

30 In step (5) of Reaction Scheme III, a 3-amino-benzyloxy[1,5]naphthyridin-4-ol of Formula XXXIV is reacted with a carboxylic acid or an equivalent thereof to provide an amide of Formula XXXV. Suitable equivalents to carboxylic acid include acid anhydrides and acid chlorides. The reaction is conveniently carried out by adding the acid chloride to a solution of a 3-amino-benzyloxy[1,5]naphthyridin-4-ol of Formula XXXIV in a suitable solvent such as dichloromethane or acetonitrile in the presence of a tertiary amine such as

triethylamine, pyridine, or 4-dimethylaminopyridine to afford an amide. The reaction can be carried out at or below ambient temperature.

In step (6) of Reaction Scheme III, a benzyloxy-[1,5]naphthyridin-4-ol of Formula XXXV is reacted with phosphorus pentasulfide to provide a benzyloxy-thiazolo[4,5-
5 c][1,5]naphthyridine Formula XXXVI. The reaction can be carried out by adding phosphorus pentasulfide to a solution or suspension of a compound of Formula XXXV in a suitable solvent such as pyridine and heating the resulting mixture.

In step (7) of Reaction Scheme III, a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridine of Formula XXXVI is oxidized to provide a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridine-
10 5*N*-oxide of Formula XXXVII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXXVI in a solvent such dichloromethane or chloroform. The reaction can be carried out at ambient temperature.

In step (8) of Reaction Scheme III, a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridine-
15 5*N*-oxide of Formula XXXVII is aminated to provide a benzyloxy-thiazolo[4,5-*c*][1,5-naphthyridin-4-amine of Formula XXXVIII. Step (8) can be carried out by the activation of an *N*-oxide of Formula XXXVII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-
20 toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide followed by *p*-toluenesulfonyl chloride to a solution of the *N*-oxide of Formula XXXVII in a suitable solvent such as 1,2-dichloroethane at
25 elevated temperature. The reaction may be carried out by adding ammonium hydroxide and *p*-toluenesulfonyl chloride to the reaction mixture from step (7) without isolating the *N*-oxide of Formula XXXVII.

Alternatively step (8) can be carried out by the reaction of a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXXVII with trichloroacetyl isocyanate followed by hydrolysis of the resulting intermediate to provide a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXVIII. The reaction is conveniently carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution

of the *N*-oxide of Formula XXXVII in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide or ammonium hydroxide at ambient temperature.

5 In step (9) of Reaction Scheme III, the benzyl group of a benzyloxy-thiazolo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXVIII is cleaved to provide a thiazolo[4,5-*c*][1,5]naphthyridinol of Formula XXXIX. The cleavage is conveniently carried out with an acid such as hydrogen bromide in a suitable solvent such as acetic acid at elevated temperature.

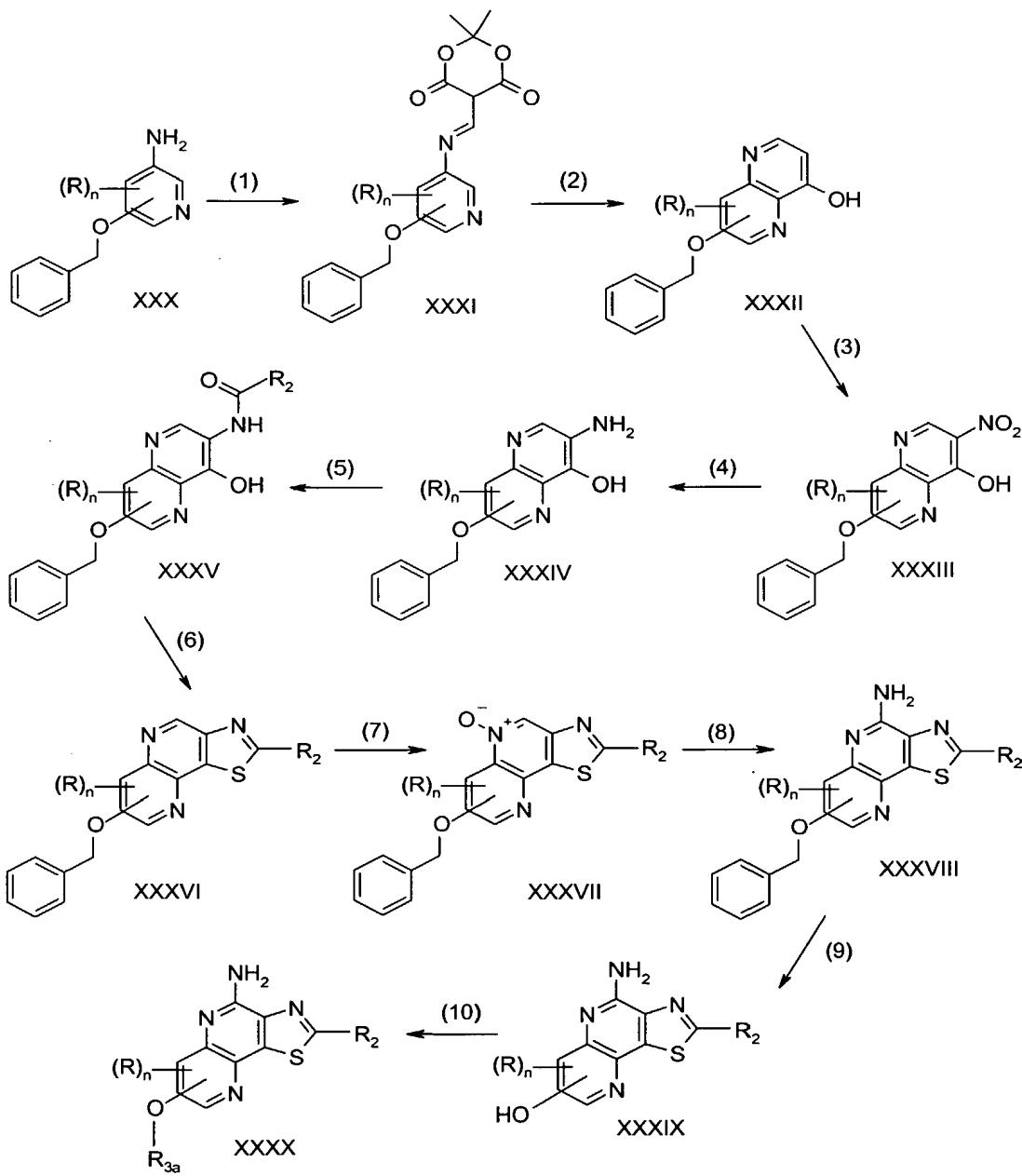
10 Alternatively, the cleavage may be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol.

15 In step (10) of Reaction Scheme III a thiazolo[4,5-*c*][1,5]naphthyridinol of Formula XXXIX is converted to an ether-substituted thiazolo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXX using a Williamson-type ether synthesis. The reaction is effected by treating a thiazolo[4,5-*c*][1,5]naphthyridinol of Formula XXXIX with an alkyl or aryl halide of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄ in the presence of a base. Numerous reagents of Formulae Halide-Z-Ar and Halide-Z-Ar'-Y-R₄ are commercially available, including substituted benzyl bromides and chlorides, substituted or 20 unsubstituted arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other reagents of Formulae Halide-Z-Ar and Halide-Z-Ar'-Y-R₄ can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining a reagent of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄ with a thiazolo[4,5-*c*][1,5]naphthyridinol of Formula XXXIX in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C, depending on the reactivity of the reagent of Formula Halide-Z-Ar or Halide-Z-Ar'-Y-R₄. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

25 Alternatively, step (10) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide of a thiazolo[4,5-*c*][1,5]naphthyridinol of Formula

XXXIX reacts with an aryl halide in the presence of copper salts, to provide compounds of Formula XXXX, where R_3 is $-Z-Ar$ or $-Z-Ar'-Y-R_4$, and Z is a bond of

Reaction Scheme III



Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound wherein R₂ is hydroxyalkylenyl can be converted into a prodrug wherein R₂ is, for example, -alkylenyl-O-C(R₆)-R₄, -alkylenyl-O-C(R₆)-O-R₄, or -alkylenyl-O-C(R₆)-N(R₈)-R₄, wherein R₄, R₆, and R₈ are as defined above, using methods known to one skilled in the art. In addition, a compound wherein Ar is substituted by hydroxy or a hydroxyalkylenyl group may also be converted to an ester, an ether, a carbonate, or a carbamate. For any of these compounds containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C₁₋₆ alkanoyloxymethyl, 1-(C₁₋₆ alkanoyloxy)ethyl, 1-methyl-1-(C₁₋₆ alkanoyloxy)ethyl, C₁₋₆ alkoxy carbonyloxymethyl, N-(C₁₋₆ alkoxy carbonyl)aminomethyl, succinoyl, C₁₋₆ alkanoyl, α -aminoC₁₋₄ alkanoyl, arylacyl, -P(O)(OH)₂, -P(O)(O-C₁₋₆ alkyl)₂, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkyl carbamoyl, and α -aminoacyl or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from racemic, D-, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from racemic, D-, or L-amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydrolysable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as -C(O)-R', α -aminoacyl, α -aminoacyl- α -aminoacyl, -C(O)-O-R', -C(O)-N(R")-R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, or -CH(CH₃)Y₁; wherein R' and R" are each independently C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, or benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylenyl, heteroarylC₁₋₄ alkylenyl, haloC₁₋₄ alkylenyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also be hydrogen; each α -aminoacyl group is independently selected from racemic, D-, and L-amino acids; Y' is hydrogen, C₁₋₆ alkyl, or benzyl; Y₀ is C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl,

mono-*N*-C₁₋₆ alkylaminoC₁₋₄ alkylene, or di-*N,N*-C₁₋₆ alkylaminoC₁₋₄ alkylene; and Y₁ is mono-*N*-C₁₋₆ alkylamino, di-*N,N*-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C₁₋₄ alkylpiperazin-1-yl.

5 **Pharmaceutical Compositions and Biological Activity**

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce, and certain compounds or salts of the invention may inhibit, the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-5 10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention 15 to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the 20 compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the 25 compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_{H1}) cytokine IFN- γ may be induced indirectly and the production of the T helper type 2 (T_{H2}) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor- α (TNF- α). Among other effects, inhibition of TNF- α production can provide prophylaxis or therapeutic treatment of TNF- α mediated diseases in animals, making the compounds or salt useful in 30 the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF- α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The

animal to which the compound or salt or composition is administered for inhibition of TNF- α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal 5 acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for 10 example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as 15 treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenza virus), a paramyxovirus 20 (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by 25 bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, 30 Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic

diseases including but not limited to malaria, pneumocystis carmii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

5 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_{H2} -mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

10 (f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

15 Additionally, a compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins;

20 glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

25 Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

5 An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise 10 amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to 15 treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition 20 is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg.

25 In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

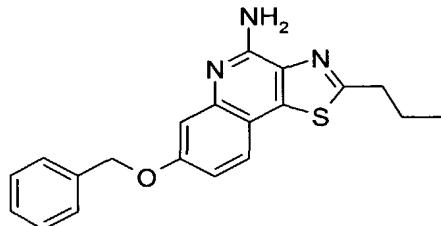
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EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

5

Example 1

7-Benzyl-2-propylthiazolo[4,5-*c*]quinolin-4-amine

Part A

10 A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzylxylaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1 °C, and the product was isolated by filtration and washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-{[(3-Benzylxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid. ¹H NMR (300MHz, DMSO-*d*₆) δ 11.21 (d, *J* = 14.2 Hz, 1H), 8.61 (d, *J* = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, *J* = 8.1, 1.96 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

Part B

20 A mixture of 5-{[(3-benzylxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was

isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder. ¹H NMR (300MHz, DMSO-*d*₆) δ 11.53 (s, 1H), 7.99 (dd, *J* = 2.4, 7.4 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, *J* = 2.5, 7.4 Hz, 1H), 5.93 (d, *J* = 7.5Hz, 1H), 5.20 (s, 2H).

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Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder. ¹H NMR (300MHz, DMSO-*d*₆) δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, *J* = 3.3, 6.3Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

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Part D

A mixture of 7-benzyloxy-3-nitroquinolin-4-ol (10.67 g, 36.0 mmol) and 5% platinum on carbon (1.05 g) in *N,N*-dimethylformamide (DMF, 110 mL) was hydrogenated on a Parr apparatus. The mixture was filtered through CELITE filter agent. The CELITE filter agent was rinsed with DMF (20 mL). The filtrate was cooled in an ice bath and acidified with hydrogen chloride gas, resulting in the formation of a reddish-brown solid. The solid was isolated by filtration, washed with acetone, and dried in a vacuum oven at 60 °C to provide 3-amino-7-benzyloxyquinolin-4-ol hydrochloride as a tan solid (8.17 g, 75%).

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Part E

To a solution of the crude 3-amino-7-benzyloxyquinolin-4-ol hydrochloride (8.03 g, 26.5 mmol) prepared in Part D and triethylamine (7.40 mL, 53 mmol) in dichloromethane at 0 °C was added butyryl chloride (2.75 mL, 26.5 mmol) dropwise *via* syringe. The solution was stirred at 0 °C for 10 minutes (min), then the cooling bath was removed. A solid formed that was isolated by filtration and washed with a small amount of dichloromethane. The solid was slurried with water (75 mL) and was isolated by filtration. The solid was rinsed with water followed by ether, then dried at 60 °C in a

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vacuum oven to provide 8.03 g (90%) of the crude product, *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)butyramide, which was contaminated with a salt of triethylamine as determined by ¹H NMR analysis.

Part F

5 A mixture of the *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)butyramide prepared in Part E (2.97 g, 8.83 mmol), P₂S₅ (1.96 g, 4.41 mmol), and pyridine was placed under a nitrogen atmosphere and heated to reflux. The resulting solution was cooled and the excess P₂S₅ was quenched slowly with 10% aqueous Na₂CO₃ (10 mL). The reaction mixture was partitioned between water (40 mL) and CH₂Cl₂ (100 mL). The organic layer 10 was washed with 0.1 M aqueous HCl (50 mL), dried over MgSO₄, filtered and concentrated to yield a brownish-yellow solid. The solid was treated with boiling heptane (40 mL) and filtered. The filtrate was allowed to cool and a solid formed. The light yellow solid was isolated by filtration and washed with cold heptane to provide 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline (1.74 g, 59%).

15 Part G

To a solution of 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline (4.89 g, 14.6 mmol) in CH₂Cl₂ (75 mL) at room temperature (rt) was added 3-chloroperoxybenzoic acid (*m*-CPBA, 65% w/w, 5.82 g, 21.93 mmol) in portions. After one hour (h), the mixture was transferred to a separatory funnel and washed with 10% aqueous Na₂CO₃ (2 x 50 mL). 20 The aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined organic layers were washed with water (75 mL), dried over MgSO₄, filtered, concentrated, and dried under high vacuum to yield 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a light yellow solid (4.93 g, 96%).

Part H

25 To a light orange solution of 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide (4.93 g, 14.1 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added trichloroacetylisocyanate (2.00 mL, 16.9 mmol). The solution was allowed to warm to rt and was stirred 20 h. The solution was concentrated *in vacuo*, and the resulting residue *N*-(7-benzyloxy-2-propylthiazolo[4,5-*c*]quinolin-4-yl)-2,2,2-trichloroacetamide was used 30 without further manipulation in the next step.

vacuum oven to provide 8.03 g (90%) of the crude product, *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)butyramide, which was contaminated with a salt of triethylamine as determined by ¹H NMR analysis.

5 Part F

A mixture of the *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)butyramide prepared in Part E (2.97 g, 8.83 mmol), P₂S₅ (1.96 g, 4.41 mmol), and pyridine was placed under a nitrogen atmosphere and heated to reflux. The resulting solution was cooled and the excess P₂S₅ was quenched slowly with 10% aqueous Na₂CO₃ (10 mL). The reaction mixture was partitioned between water (40 mL) and CH₂Cl₂ (100 mL). The organic layer 10 was washed with 0.1 M aqueous HCl (50 mL), dried over MgSO₄, filtered and concentrated to yield a brownish-yellow solid. The solid was treated with boiling heptane (40 mL) and filtered. The filtrate was allowed to cool and a solid formed. The light yellow solid was isolated by filtration and washed with cold heptane to provide 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline (1.74 g, 59%).

15 Part G

To a solution of 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline (4.89 g, 14.6 mmol) in CH₂Cl₂ (75 mL) at room temperature (rt) was added 3-chloroperoxybenzoic acid (*m*-CPBA, 65% w/w, 5.82 g, 21.93 mmol) in portions. After one hour (h), the mixture was transferred to a separatory funnel and washed with 10% aqueous Na₂CO₃ (2 x 50 mL). 20 The aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined organic layers were washed with water (75 mL), dried over MgSO₄, filtered, concentrated, and dried under high vacuum to yield 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a light yellow solid (4.93 g, 96%).

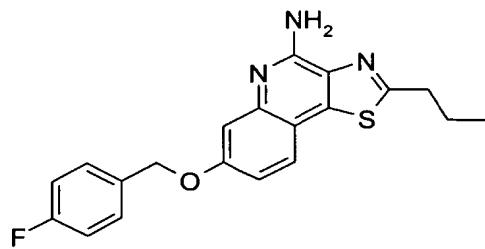
Part H

25 To a light orange solution of 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide (4.93 g, 14.1 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added trichloroacetylisocyanate (2.00 mL, 16.9 mmol). The solution was allowed to warm to rt and was stirred 20 h. The solution was concentrated *in vacuo*, and the resulting residue *N*-(7-benzyloxy-2-propylthiazolo[4,5-*c*]quinolin-4-yl)-2,2,2-trichloroacetamide was used 30 without further manipulation in the next step.

Part I

To a magnetically stirred mixture of *N*-(7-benzyloxy-2-propylthiazolo[4,5-*c*]quinolin-4-yl)-2,2,2-trichloroacetamide (prepared as described above in Part H, 6.96 g, 14.9 mmol) in methanol (100 mL) at rt was added NaOMe (25 wt. % solution in MeOH, 11.3 mL, 52.1 mmol). After a few minutes a solution formed from which a solid precipitated. The reaction mixture was concentrated *in vacuo* and dried under vacuum. The resulting solid was suspended in a minimal amount of methanol (50 mL) and was isolated by filtration. The solid was washed with methanol to provide 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinolin-4-amine as a light yellow solid in high purity (3.93 g, 76%), mp 175-178 °C. ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.67 (d, *J* = 8.7 Hz, 1H), 7.49-7.29 (m, 5H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.84 (s, 2H), 5.20 (s, 2H), 3.09 (t, *J* = 7.8 Hz, 2H), 1.84 (sextet, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, *d*₆-DMSO) δ 169.1, 158.9, 152.4, 146.5, 139.4, 137.0, 136.0, 128.4, 127.8, 127.6, 125.7, 113.3, 113.2, 107.8, 69.3, 35.1, 22.8, 13.5. MS (APCI) *m/z* = 350.0 (M + H)⁺; Anal. calcd for C₂₀H₁₉N₃OS: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.62; H, 5.74; N, 11.94.

Example 2

7-(4-Fluorobenzyloxy)-2-propylthiazolo[4,5-*c*]quinolin-4-amine

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Part A

To 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinoline (prepared as described in Part F of Example 1, 4.52 g, 13.5 mmol) was added a 45 wt.% solution of hydrogen bromide in acetic acid (40 mL). The resulting solution was heated at 65 °C for 1.5 h, then cooled in an ice bath. Aqueous NaOH (50% w/w solution) was added slowly until the pH = 7 and a light yellow solid formed. The solid was isolated by filtration, dried, and then suspended in boiling ethanol (25 mL) for 5 min. The mixture was allowed to cool to rt and a tan solid

was isolated by filtration. The solid was washed with cold ethanol and dried in a vacuum oven to yield 7-hydroxy-2-propylthiazolo[4,5-*c*]quinoline (2.69 g, 82%).

Part B

5 A mixture of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinoline (0.88 g, 3.6 mmol) and cesium carbonate (2.35 g, 7.20 mmol) in DMF (50 mL) was stirred for 30 min, then 4-fluorobenzylbromide (0.50 mL, 4.0 mmol) was added. After 2 h, the mixture was concentrated *in vacuo* to remove the DMF. The resulting solid was partitioned between dichloromethane (100 mL) and water (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated to a light yellow solid. The solid was recrystallized from heptane and pure 7-(4-fluorobenzylxy)-2-propylthiazolo[4,5-*c*]quinoline was isolated as a tan solid (0.86 g, 68%).

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Part C

15 7-(4-Fluorobenzylxy)-2-propylthiazolo[4,5-*c*]quinoline (0.84 g, 2.38 mmol) was treated with *m*-CPBA (65% w/w, 0.95 g, 3.58 mmol) according to the method described in Part G of Example 1 to yield 7-(4-fluorobenzylxy)-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a light yellow solid (0.81 g, 92%).

Part D

20 To a solution of 7-(4-fluorobenzylxy)-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide (0.81 g, 2.2 mmol) in 1,2-dichloroethane at 65 °C in a glass heavy wall pressure vessel was added concentrated ammonium hydroxide (5 mL) and *p*-toluenesulfonyl chloride (0.42 g, 2.4 mmol). The vessel was sealed with a screw cap and the mixture was stirred at 65 °C for 3 h. The reaction mixture was transferred to a separatory funnel with dichloromethane (50 mL) and washed with 2 M aqueous Na₂CO₃ (2 x 50 mL). The combined aqueous layers were extracted with dichloromethane (50 mL). The organic phases were combined, washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered and concentrated to yield a brown solid. The crude product was purified on a HORIZON High-Performance Flash Chromatography (HPFC) instrument (available from Biotage, Inc, Charlottesville, Virginia, USA) (silica gel eluting sequentially with 0-15% of a solution comprised of 80% CHCl₃, 18% MeOH, and 2% conc. NH₄OH (CMA) in chloroform). The appropriate fractions were combined and concentrated to provide a light yellow solid. The solid was crystallized from acetonitrile. The resulting white solid was isolated, washed with acetonitrile, and dried overnight at 60 °C in a vacuum oven to

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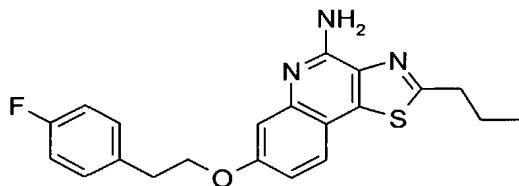
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provide 7-(4-fluorobenzyloxy)-2-propylthiazolo[4,5-*c*]quinolin-4-amine (0.33 g, 41%), mp 189-192 °C. ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.67 (d, *J* = 8.8 Hz, 1H), 7.55-7.50 (m, 2H), 7.26-7.18 (m, 2H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.80 (s, 2H), 5.20 (s, 2H), 3.11 (t, *J* = 7.8 Hz, 2H), 1.84 (sextet, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); Anal. calcd for C₂₀H₁₈N₃OSF: C, 65.38; H, 4.94; N, 11.44. Found: C, 65.36; H, 4.87; N, 11.39.

Example 3

7-[2-(4-Fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine

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Part A

Iodine (12.0 g, 47.4 mmol) was added in one portion to a solution of 2-phenylethanol (5.11 g, 36.5 mmol), triphenylphosphine (11.47 g, 43.8 mmol) and imidazole (3.48 g, 51.04 mmol) in dichloromethane (250 mL) at 0 °C. The resulting mixture was allowed to warm slowly to rt and stir overnight, then was transferred to a separatory funnel and washed with water (2 x 250 mL), saturated aqueous Na₂S₂O₃ (2 x 100 mL), water (100 mL), and brine (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated to a colorless oil that contained a large amount of white solid. The mixture was treated with heptane (2 x 50 mL) and was filtered. The filtrate was concentrated and the resulting material was again treated with heptane (2 x 50 mL) and filtered. The filtrate was concentrated to provide 2-phenylethyl iodide as a clear colorless oil (1.74 g, 19 %) that contained a trace amount of triphenylphosphine oxide.

Part B

A mixture of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinoline (prepared as described in Part A of Example 2, 0.94 g, 3.9 mmol) and cesium carbonate (2.07 g, 6.36 mmol) in DMF (25 mL) was heated at 75 °C for 20 min, then a solution of 2-phenylethyl iodide (1.06 g, 4.24 mmol) in DMF (10 mL) was added dropwise. The solution was heated at 75 °C for 4 d. The DMF was removed *in vacuo* and the resulting solid was partitioned

between chloroform (100 mL) and water (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated to a dark brown solid. The solid was purified by HPFC (silica gel eluting sequentially with 0-8% CMA in chloroform). The appropriate fractions were combined and concentrated to provide 7-[2-(4-fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline as a light yellow solid (0.27 g, 19%).

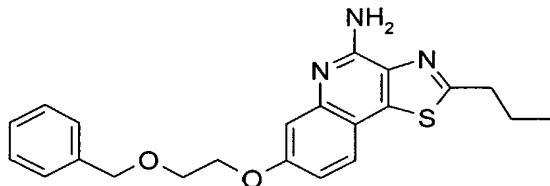
5 Part C

10 7-[2-(4-Fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline (0.29 g, 0.79 mmol) was treated with *m*-CPBA (65% w/w, 0.32 g, 1.2 mmol) according to the method described in Part G of Example 1 to yield 7-[2-(4-fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a light orange solid (0.30 g, 100%).

Part D

15 7-[2-(4-Fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide (0.30 g, 0.78 mmol) was treated with concentrated ammonium hydroxide (4 mL) and *p*-toluenesulfonyl chloride (0.17 g, 0.86 mmol) according to the method described in Part D of Example 2. The crude product was purified by HPFC (silica gel eluting sequentially with 0-15% CMA in chloroform). The appropriate fractions were combined and concentrated to provide a light yellow solid. The solid was crystallized from acetonitrile. The resulting white solid was isolated, washed with acetonitrile, and dried overnight at 60 °C in a vacuum oven to provide 7-[2-(4-fluorophenyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine (0.13 g, 43%), mp 145-148 °C. ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.67 (d, *J* = 8.7 Hz, 1H), 7.40-7.34 (m, 2H), 7.17-7.09 (m, 2H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.79 (s, 2H), 4.27 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 7.8 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H), 1.82 (sextet, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); Anal. 20 calcd for C₂₁H₂₀N₃OSF: C, 66.12; H, 5.28; N, 11.02. Found: C, 66.19; H, 5.26; N, 11.03.

Example 4

7-[2-(Benzylloxy)ethoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine

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Part A

A solution of 2-(benzylloxy)ethanol (5.12 g, 33.6 mmol), triphenylphosphine (10.59 g, 40.4 mmol), and imidazole (3.21 g, 47.1 mmol) in dichloromethane (250 mL) was treated with iodine (11.10 g, 43.7 mmol) according to the method described in Part A of Example 3 to yield benzyl 2-iodomethyl ether as a clear colorless oil (5.95 g, 68%) that contained a trace amount of triphenylphosphine oxide.

Part B

A mixture of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinoline (prepared as described in Part A of Example 2, 0.66 g, 2.7 mmol) and cesium carbonate (1.32 g, 4.05 mmol) in DMF (25 mL) was heated at 75 °C for 30 min, then a solution of benzyl 2-iodomethyl ether (1.42 g, 5.40 mmol) in DMF (5 mL) was added dropwise. The solution was heated at 75 °C for 16 h. The DMF was removed *in vacuo* and the resulting solid was partitioned between chloroform (100 mL) and water (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated to a dark brown solid. The solid was purified by HPFC (silica gel eluting sequentially with 0-8% CMA in chloroform). The appropriate fractions were combined and concentrated to provide 7-[2-(benzylloxy)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline as a light yellow solid (0.89 g, 87%).

Part C

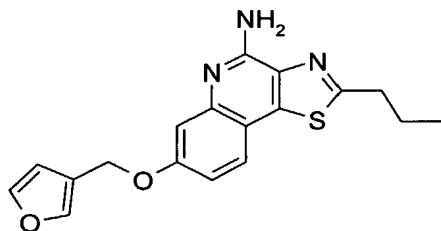
7-[2-(Benzylloxy)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline (0.89 g, 2.35 mmol) was treated with *m*-CPBA (65% w/w, 0.94 g, 3.53 mmol) according to the method described in Part G of Example 1 to yield 7-[2-(benzylloxy)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a light yellow solid (0.85 g, 91%).

Part D

7-[2-(Benzyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide (0.85 g, 2.15 mmol) was treated with concentrated ammonium hydroxide (5 mL) and *p*-toluenesulfonyl chloride (0.45 g, 2.37 mmol) according to the method described in Part D of Example 2.

5 The crude product was purified by HPFC (silica gel eluting sequentially with 0-15% CMA in chloroform). The appropriate fractions were combined and concentrated to provide a light yellow solid. The solid was crystallized from acetonitrile. The resulting white solid was isolated by filtration, washed with acetonitrile, and dried overnight at 60 °C in a vacuum oven to provide 7-[2-(benzyl)ethoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine (0.29 g, 34%) as off-white needles, mp 142-145 °C. ¹H NMR (300 MHz, *d*₆-DMSO) δ 7.67 (d, *J* = 8.8 Hz, 1H), 7.37-7.24 (m, 5H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.80 (s, 2H), 4.57 (s, 2H), 4.24-4.21 (m, 2H), 3.82-3.79 (m, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 1.84 (sextet, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, *d*₆-DMSO) δ 169.0, 159.1, 152.4, 146.5, 139.36, 138.3, 136.0, 128.2, 127.5, 127.4, 125.7, 113.1, 107.3, 72.1, 68.2, 67.1, 35.1, 22.8, 13.4; Anal. calcd for C₂₂H₂₃N₃O₂S: C, 67.15; H, 5.89; N, 10.68. Found: C, 67.11; H, 5.77; N, 10.48.

Example 5

7-(Furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinolin-4-amine

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Part A

Diisopropyl azodicarboxylate (1.51 g, 7.5 mmol) was added to a mixture of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinoline (prepared as described in Part A of Example 2, 920 mg, 3.76 mmol) and triphenylphosphine (1.96 g, 7.5 mmol) in THF (50 mL). The mixture was stirred overnight. The following morning, additional reagents were added to the solution and stirring was continued for 3 h. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane and washed with 2% aqueous Na₂CO₃ (3 x 50 mL). The aqueous phases were combined and extracted multiple times with chloroform.

The organic phases were combined, dried over MgSO₄, filtered, and concentrated. The crude product was purified by HPFC (silica gel eluting with a dichloromethane/methanol gradient). All fractions containing the product 7-(furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinoline were combined, concentrated, and carried on to the next step without further purification.

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Part B

7-(Furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinoline (prepared as described above in Part A, 3.76 mmol) was treated with *m*-CPBA (60% w/w, 1.60 g, 5.65 mmol) according to the method described in Part G of Example 1 to yield 7-(furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinoline-5*N*-oxide as a solid. The solid was dissolved in dichloromethane (100 mL) and trichloroacetyl isocyanate (777 mg, 4.13 mmol) was added dropwise to the solution. After all the starting material was consumed in the reaction, concentrated ammonium hydroxide (2 mL) was added. After several minutes the mixture was concentrated *in vacuo* and the residue was purified by HPFC (silica gel with a gradient elution using 0-15% CMA in chloroform). The appropriate fractions were combined and concentrated to a solid. The solid was dissolved in dichloromethane and loaded onto an acid ion-exchange resin. The resin was washed with methanol (2 x 40 mL). The 7-(furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinolin-4-amine was eluted with a solution of 2 M ammonia in methanol (2 x 40 mL). The filtrate was concentrated *in vacuo* and pure 7-(furan-3-ylmethoxy)-2-propylthiazolo[4,5-*c*]quinolin-4-amine was obtained as an off-white crystals, mp 170.0-171.0 °C (143 mg, 12%) after crystallization from acetonitrile. MS (APCI) *m/z* 340 (M + H)⁺; Anal. calcd for C₁₈H₁₇N₃O₂S: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.38; H, 5.08; N, 12.56.

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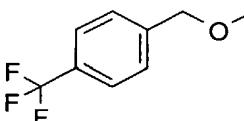
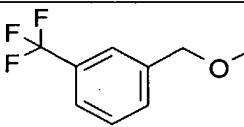
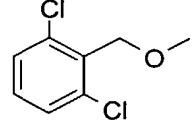
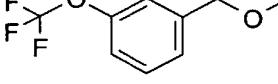
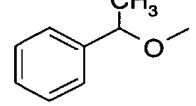
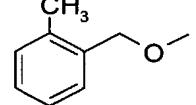
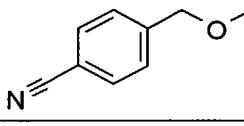
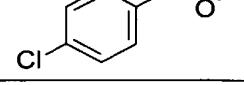
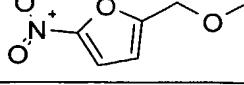
Examples 6-28

To 7-benzyloxy-2-propylthiazolo[4,5-*c*]quinolin-4-amine (prepared as described in Example 1, 1.59 g, 4.55 mmol) was added a 30 wt.% solution of hydrogen bromide in acetic acid (25 mL). The resulting solution was heated at 65 °C for 1 h, then cooled in an ice bath. Aqueous NaOH (50% w/w solution) was added slowly until the pH = 7 and a light yellow solid formed. The solid was isolated by filtration, dried, and purified by HPFC (silica gel eluting sequentially with 0-10% of a solution comprised of 80% CHCl₃, 18% MeOH, and 2% conc. NH₄OH (CMA) in chloroform, then 10-35% CMA in

chloroform). The appropriate fractions were concentrated to a light yellow solid that was crystallized from toluene containing a small amount of methanol. The light yellow solid was isolated by filtration, washed with cold toluene, and dried at 60 °C in a vacuum oven to provide the acetic acid salt of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinolin-4-amine (0.64 g, 54 %), mp 236-239 °C. ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.72 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 2.2 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.70 (s, 2H), 3.12 (t, *J* = 7.8 Hz, 2H), 1.83 (sextet, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, *d*₆-DMSO) δ 168.4, 158.1, 152.2, 146.6, 139.6, 135.6, 125.7, 113.3, 112.2, 108.9, 35.0, 22.8, 13.4; Anal. calcd for C₁₃H₁₃N₃OS•0.22 C₂H₄O₂: C, 59.23; H, 5.13; N, 15.42. Found: C, 59.42; H, 5.00; N, 15.41.

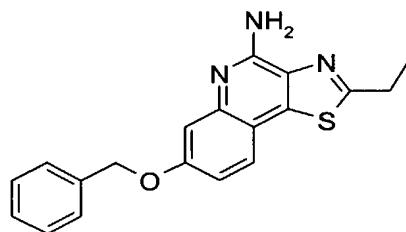
Aliquots (1 mL, 0.1 mmol) of an anhydrous dimethylformamide solution (39 mL) of 7-hydroxy-2-propylthiazolo[4,5-*c*]quinolin-4-ylamine (1.01 g, 3.9 mmol) were transferred to test tubes containing anhydrous potassium carbonate (55 mg, 0.4 mmol). Appropriate amounts of the alkylating agents (1.1 equivalents) listed below were added to the test tubes and the test tubes were shaken overnight. A filtration plate was used to remove the potassium carbonate from the reaction mixtures and the filtrates were collected in a 2.2 mL/well titre plate. The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Zorbax BonusRP, 21.2 x 50 millimeters (mm), 5 micron particle size; non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

| Example | Reagent | R_3 | Measured Mass ($M+H$) |
|---------|-----------------------------------|-------|-------------------------|
| 6 | Benzyl bromide | | 350.1351 |
| 7 | α -Bromo- <i>m</i> -xylene | | 364.1489 |
| 8 | 2-Cyanobenzyl bromide | | 375.1294 |
| 9 | 2-Chlorobenzyl bromide | | 384.0940 |
| 10 | 3-Chlorobenzyl bromide | | 384.0964 |
| 11 | 2,3-Difluorobenzyl bromide | | 386.1135 |
| 12 | 2,4-Difluorobenzyl bromide | | 386.1138 |
| 13 | 2,6-Difluorobenzyl bromide | | 386.1146 |
| 14 | 3,4-Difluorobenzyl bromide | | 386.1156 |
| 15 | 4-Nitrobenzyl bromide | | 395.1208 |

| Example | Reagent | R_3 | Measured Mass ($M+H$) |
|---------|------------------------------------|---|-------------------------|
| 16 | 4-(Trifluoromethyl)benzyl bromide |  | 418.1194 |
| 17 | 2-(Trifluoromethyl)benzyl bromide |  | 418.1221 |
| 18 | 3-(Trifluoromethyl)benzyl bromide |  | 418.1209 |
| 19 | 2,6-Dichlorobenzyl bromide |  | 418.0553 |
| 20 | 3-(Trifluoromethoxy)benzyl bromide |  | 434.1153 |
| 21 | (1-Bromoethyl)benzene |  | 364.1512 |
| 22 | α -Bromo- <i>o</i> -xylene |  | 364.1486 |
| 23 | 4-Cyanobenzyl bromide |  | 375.1289 |
| 24 | 4-Chlorobenzyl bromide |  | 384.0956 |
| 25 | 2-(Bromomethyl)-5-nitrofuran |  | 385.0987 |

| Example | Reagent | R ₃ | Measured Mass (M+H) |
|---------|---|----------------|---------------------|
| 26 | 2-(Bromomethyl)naphthalene | | 400.1487 |
| 27 | Methyl 4-(bromomethyl)benzoate | | 408.1399 |
| 28 | Methyl <i>alpha</i> -bromophenylacetate | | 408.1386 |

Example 29

7-Benzyl-2-ethylthiazolo[4,5-*c*]quinolin-4-amine

5

Part A

A 1 L glass Parr bottle was charged with 7-benzyl-3-nitroquinolin-7-ol, anhydrous *N,N*-dimethylformamide (DMF, 500 mL) and 5% Pt/C catalyst (5.0 g). The vessel was placed on Parr apparatus, evacuated and charged with hydrogen gas (~45 psi, 3.1×10^5 Pa). The reaction mixture was shaken overnight. The reaction mixture was filtered through glass fiber filters to remove catalyst. To the resulting dark colored solution was added concentrated hydrochloric acid (12 N HCl, 14 ml, 168.8 mmol). The product precipitated as the hydrochloride salt. The reaction mixture was stirred over the

weekend. A solid was collected by vacuum filtration, washed with diethyl ether (100 mL), and air dried overnight to provide 44 g of 3-amino-7-benzyloxyquinolin-4-ol hydrochloride. This material was carried on without further purification.

Part B

5 To a stirred solution of 3-amino-7-benzyloxyquinolin-4-ol hydrochloride (40.4 g, 133.4 mmol), and triethylamine (2.5 eq., 33.8 g, 333.6 mmol) in dichloromethane (1000mL) at room temperature, was slowly added propionyl chloride (1.1 eq., 13.6 g, 146.8 mmol). After 6 hours the reaction was quenched with water (250 ml). The reaction mixture was transferred to a separatory funnel and the layers were separated. The 10 dichloromethane layer was concentrated to provide 41.5 g of *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)propionamide as a pale tan crystalline solid. MS (ACPI) *m/z*=323 (M + H)⁺. This material was carried on without further purification to the next step.

Part C

15 To a stirred slurry of *N*-(7-benzyloxy-4-hydroxyquinolin-3-yl)propionamide in pyridine 500 (mL) was added 0.5 eq. phosphorous pentasulfide (28.6 g, 64.4 mmol). The reaction mixture was heated to reflux. The reaction mixture became homogeneous (dark orange) as the reaction heated to reflux. The reaction was maintained at reflux overnight. The reaction mixture was cooled to room temperature and the excess phosphorous pentasulfide was slowly quenched with 10% aqueous sodium carbonate (50 mL). The 20 reaction mixture was transferred to a separatory funnel and partitioned between water (200 mL) and dichloromethane (700 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 100 mL). The organic layers were combined and concentrated to dryness. The resulting tan solid was treated with boiling heptane (3 x 400 mL) and filtered. The heptane filtrates were combined and concentrated to provide 15 g of 25 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinoline as a pale yellow crystalline solid. MS (ACPI) *m/z*=321 (M + H)⁺. This material was carried on without further purification to the next step.

Part D

30 To a stirred solution of 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinoline (15.0 g, 46.8 mmol) in chloroform (150 mL), 3-chloroperoxybezoic acid (m-CPBA. 50% w/w, 16.15 g, 46.8 mmol) was slowly added in small portions. The reaction was maintained at room temperature overnight. The reaction mixture was transferred to a separatory funnel and

washed with 10% aqueous sodium carbonate (2 x 50 mL). The chloroform layer was concentrated to provide 15.4 g of 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinoline 5-oxide as a light tan solid. MS (ACPI) *m/z*=337 (M + H)⁺. This material was carried on without further purification to the next step.

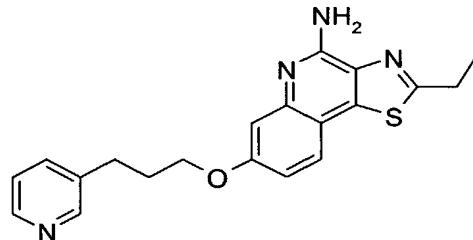
5 Part E

To a vigorously stirred pale orange solution of 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinoline 5-oxide (15.00 g, 44.6 mmol) in dichloromethane (200 mL), at room temperature, was slowly added trichloroacetylisocyanate (1.05 eq., 5.6 ml 46.8 mmol). The solution was maintained at room temperature for 18 hours. At this time the reaction 10 was quenched by the addition of concentrated ammonium hydroxide solution (60 ml). An off-white precipitate formed and was collected by vacuum filtration. Recrystallization from acetonitrile provided 11.3 g of 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as a white crystalline solid, mp 208-209 °C. MS (APCI) *m/z* 336.1 (M + H)⁺; Anal. calcd for C₁₉H₁₇N₃OS: C, 68.03; H, 5.11; N, 12.53. Found: C, 67.45; H, 4.83; N, 12.41.

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Example 30

2-Ethyl-7-[3-(pyridin-3-yl)propoxy]thiazolo[4,5-*c*]quinolin-4-amine



20 Part A

To a round bottom flask containing 7-benzyloxy-2-ethylthiazolo[4,5-*c*]quinolin-4-amine (11.3 g, 33.7 mmol) was added a 45 wt.% solution of hydrogen bromide in acetic acid (40 mL). The resulting solution was heated at 65 °C for 2 hours and then cooled in an ice bath. Aqueous sodium hydroxide (50% w/w solution) was added slowly until pH 7 25 and a pale yellow/green solid formed. The solid was isolated by filtration and air dried to provide 8.4 g of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol. MS (APCI) *m/z*=246.0.

Part B

To a stirred solution (pale orange) of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (0.24 g, 1.0 mmol) was dissolved in anhydrous DMF (5 mL) was added cesium carbonate (3.0 eq., 1.0 g, 3.0 mmol) and 1.1 eq. of an 80% solution of propargyl bromide in toluene (0.16 g). The mixture was heated to 65 °C and maintained overnight. The reaction was quenched by slowly adding the reaction mixture to 10 volumes of water (50 mL). The resulting solid was collected by vacuum filtration, rinsed with acetonitrile and air dried, to provide 0.22 g of 2-ethyl-7-[(prop-2-ynyl)oxy]thiazolo[4,5-*c*]quinolin-4-amine as a pale-peach colored crystalline solid. MS (ACPI) *m/z*=284 (M + H)⁺.

10 Part C

To a stirred solution of 2-ethyl-7-[(prop-2-ynyl)oxy]thiazolo[4,5-*c*]quinolin-4-amine (0.18 g, 0.635 mmol), and triethylamine (3.0 eq. 0.27 ml, 1.9 mmol) dissolved in anhydrous DMF (5 mL) was added a solution of 3-iodopyridine (1.1 eq. 0.14 g, 0.699 mmol), copper iodide (0.04 eq., 4.8 mg, 0.025 mmol), and PdCl₂(PPh₃)₂ (0.02 eq., 9.12 mg, 0.013 mmol) in anhydrous DMF (10 mL). The reaction mixture was heated to 65 °C under a nitrogen atmosphere for 24 hours. The reaction was quenched by slowly pouring it into water (100 ml). The mixture was extracted with dichloromethane (4 x 25 ml). The organic fractions were combined and concentrated to dryness. The resulting solid was recrystallized from acetonitrile to provide 0.19 g of 2-ethyl-7-{[(3-(pyridin-3-yl)prop-2-ynyl)oxy]thiazolo[4,5-*c*]quinolin-4-amine. MS (APCI) *m/z*=361.1 (M+H).

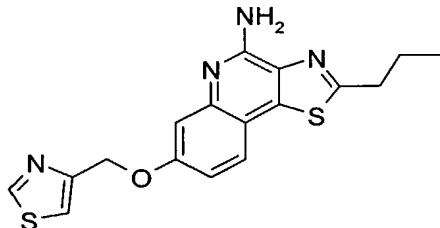
20 Part D

A glass Parr vessel was charged with a golden solution of 2-ethyl-7-{[(3-(pyridin-3-yl)prop-2-ynyl)oxy]thiazolo[4,5-*c*]quinolin-4-amine in 1:1 ethyl acetate:ethanol (150 mL), and 10% Pd/C catalyst (20 mg). The reaction vessel was evacuated and charged with 25 hydrogen (~50 psi, 3.4 X 10⁵ Pa). The mixture was shaken for 10 hours at ambient temperature. At this time the reaction was analyzed by thin layer chromatography (10% methanol in dichloromethane) and found to be incomplete. The reaction vessel was recharged with additional catalyst (23 mg) and hydrogen (~50 psi, 3.4 X 10⁵ Pa) and shaken an additional 48 hours. The reaction mixture was filtered to remove catalyst, and then 30 concentrated to dryness. The desired product was purified by HPFC (eluting with a gradient of 0-20% CMA in chloroform, (1440 ml)), followed by recrystallization from

acetonitrile, to provide 0.1 g of 2-ethyl-7-[3-(pyridin-3-yl)propoxy]thiazolo[4,5-*c*]quinolin-4-amine as off white crystals, mp 172-173 °C. MS (APCI) *m/z* 365 (M + H)⁺.

Example 31

5 2-Propyl-7-[(thiazol-4-yl)methoxy]thiazolo[4,5-*c*]quinolin-4-amine

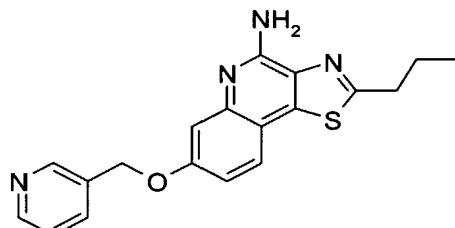


A mixture of 4-amino-2-propylthiazolo[4,5-*c*]quinolin-7-ol acetate (318 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), and DMF (15 mL) was stirred at 75 °C for 10 minutes. 4-(Chloromethyl)thiazole hydrochloride (187 mg, 1.1 mmol) was added. Additional 4-(chloromethyl)thiazole hydrochloride (1 eq. total) was added in small portions over a period of 3 hours. The reaction mixture was poured into water (100 mL). A solid was isolated by filtration, allowed to dry, dissolved in dichloromethane, and then purified by HPFC eluting with a gradient of 0 – 25 % CMA in chloroform over 1400 mL and then 25 % CMA in chloroform over 600 mL. The resulting solid was recrystallized from acetonitrile to provide 200 mg of 2-propyl-7-[(thiazol-4-yl)methoxy]thiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 218.0-220.0 °C. MS (APCI) *m/z* 357 (M + H)⁺; Anal. calcd for C₁₇H₁₆N₄OS₂•0.2 H₂O: C, 56.71; H, 4.59; N, 15.56. Found C, 56.66; H, 4.29; N, 15.45.

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Example 32

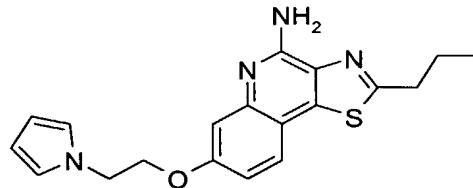
2-Propyl-7-[(pyridin-3-yl)methoxy]thiazolo[4,5-*c*]quinolin-4-amine



A mixture of 4-amino-2-propylthiazolo[4,5-*c*]quinolin-7-ol acetate (318 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 3-(Iodomethyl)pyridine hydroiodide (381 mg, 1.1 mmol) was added in portions over a period of 3 hours. The heat source was removed and the reaction mixture was 5 stirred at ambient temperature overnight. The reaction mixture was diluted with water (250 mL), stirred for 1 hour, and then filtered. The isolated solid was rinsed with water and then dried to provide a brown powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0 – 20 % CMA in chloroform over 1400 mL and then 20 % CMA in chloroform over 600 mL. The resulting 10 solid was recrystallized from acetonitrile to provide 160 mg of 2-propyl-7-[(pyridin-3-yl)methoxy]thiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 167.0–169.0 °C. MS (APCI) *m/z* 351 (M + H)⁺; Anal. calcd for C₁₉H₁₈N₄OS: C, 65.12; H, 5.18; N, 15.99. Found C, 65.25; H, 5.06; N, 16.03.

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Example 33

2-Propyl-7-[2-(pyrrol-1-yl)ethoxy]thiazolo[4,5-*c*]quinolin-4-amine

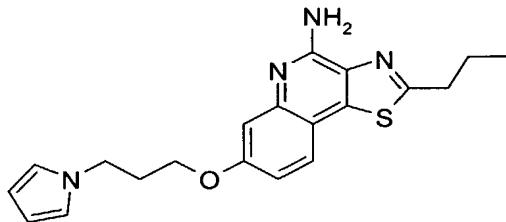
A mixture of 4-amino-2-propylthiazolo[4,5-*c*]quinolin-7-ol acetate (318 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 1-(2-Bromoethyl)pyrrole (200 mg, 1.1 mmol) was added dropwise over a period of 10 minutes. After 3 hours an additional equivalent of cesium carbonate was added in a single portion followed by the dropwise addition of an equivalent of 1-(2-bromoethyl)pyrrole. The reaction mixture was stirred overnight and then an additional equivalent of both cesium carbonate and 1-(2-bromoethyl)pyrrole were added. After 1 20 hour the heat source was removed; the reaction mixture was diluted with water (250 mL), stirred for 1 hour, and then filtered. The isolated solid was rinsed with water and then dried to provide a brown powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0 – 15 % CMA in chloroform over 1500 25

mL. The resulting solid was recrystallized from acetonitrile to provide 143 mg of 2-propyl-7-[2-(pyrrol-1-yl)ethoxy]thiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 158.0-160.0 °C. MS (ESI) *m/z* 353 (M + H)⁺; Anal. calcd for C₁₉H₂₀N₄OS: C, 64.75; H, 5.72; N, 15.90. Found C, 64.86; H, 5.38; N, 16.00.

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Example 34

2-Propyl-7-[3-(pyrrol-1-yl)propoxy]thiazolo[4,5-*c*]quinolin-4-amine

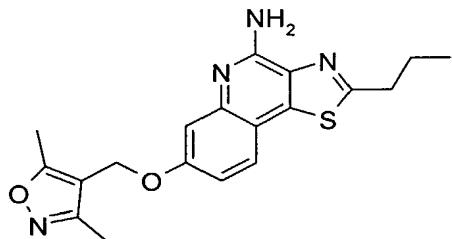


10 A mixture of 4-amino-2-propylthiazolo[4,5-*c*]quinolin-7-ol acetate (318 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 1-(2-Bromopropyl)pyrrole (206 mg, 1.1 mmol) was added dropwise over a period of 10 minutes. After 3 hours an additional equivalent of cesium carbonate was added in a single portion followed by the dropwise addition of an equivalent of 1-(2-bromopropyl)pyrrole. After 1 additional hour the heat source was removed; the reaction mixture was diluted with water (250 mL), stirred for 1 hour, and then filtered. The isolated solid was rinsed with water and then dried to provide a brown powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0 – 20 % CMA in chloroform over 1500 mL. The resulting solid was recrystallized from acetonitrile to provide 168 mg of 2-propyl-7-[3-(pyrrol-1-yl)propoxy]thiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 152.0-154.0 °C. MS (ESI) *m/z* 367 (M + H)⁺; Anal. calcd for C₂₀H₂₂N₄OS: C, 65.55; H, 6.05; N, 15.29. Found C, 65.52; H, 5.80; N, 15.37.

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Example 35

7-[(3,5-Dimethylisoxazol-4-yl)methoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine

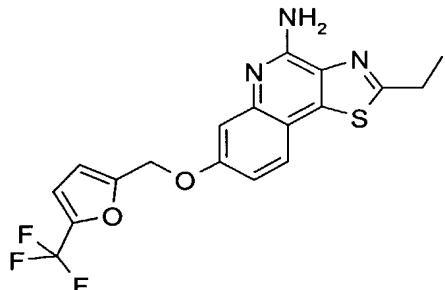
5 A mixture of 4-amino-2-propylthiazolo[4,5-*c*]quinolin-7-ol acetate (318 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 4-(Chloromethyl)-3,5-dimethylisoxazole (160 mg, 1.1 mmol) was added dropwise over a period of 10 minutes. After 3 hours an additional equivalent of cesium carbonate was added in a single portion followed by the dropwise addition of an equivalent of 4-(chloromethyl)-3,5-dimethylisoxazole . After 1 additional hour the heat source was removed; the reaction mixture was diluted with water (250 mL), stirred for 1 hour, and then filtered. The isolated solid was rinsed with water and then dried to provide a brown powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0 – 5% methanol in dichloromethane for over 1000 mL and then with 5% methanol in dichloromethane over 400 mL. The resulting solid was recrystallized from acetonitrile to provide 156 mg of 7-[(3,5-dimethylisoxazol-4-yl)methoxy]-2-propylthiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 178.0-180.0 °C. MS (ESI) *m/z* 369 (M + H)⁺; Anal. calcd for C₁₉H₂₀N₄O₂S: C, 61.94; H, 5.47; N, 15.21. Found C, 61.98; H, 5.25; N, 15.26.

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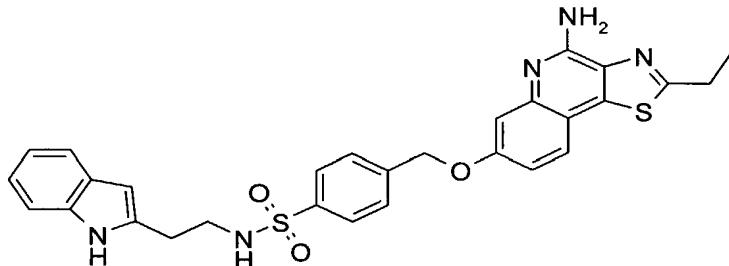
Example 36

2-Ethyl-7-{{[5-(trifluoromethyl)furan-2-yl]methoxy}thiazolo[4,5-*c*]quinolin-4-amine

5 A mixture of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (245 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 2-(Bromomethyl)-5-(trifluoromethyl)furan (252 mg, 1.1 mmol) was added in portions over a period of 30 minutes. The reaction mixture was stirred for 1 hour and then the heat source was removed. The reaction mixture was diluted with water (250 mL),
10 stirred for 1 hour, and then filtered. The isolated solid was rinsed with water and then dried to provide a brown powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0- 15 % CMA in chloroform 700 mL and then with 15 % CMA in chloroform over 200 mL. The resulting solid was recrystallized from acetonitrile to provide 125 mg of 2-ethyl-7-{{[5-(trifluoromethyl)furan-2-
15 yl]methoxy}thiazolo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 152-154 °C. MS (ESI) *m/z* 394 (M + H)⁺; Anal. calcd for C₁₈H₁₄F₃N₃O₂S: C, 54.96; H, 3.59; N, 10.68. Found: C, 54.90; H, 3.46; N, 10.52.

Example 37

4-{{(4-Amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]methyl}-*N*-[2-(1*H*-indol-2-yl)ethyl]benzenesulfonamide



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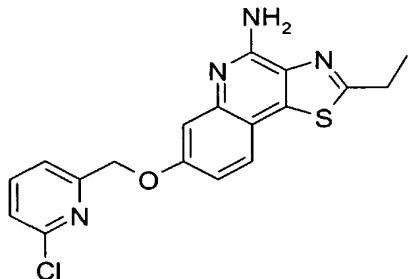
A mixture of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (245 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. {[4-(Bromomethyl)phenyl]sulfonyl}[2-(indol-3-yl)ethyl]amine (432 mg, 1.1 mmol) was added in portions over a period of 30 minutes. Several small additions of {[4-(bromomethyl)phenyl]sulfonyl}[2-(indol-3-yl)ethyl]amine were made over several hours. The reaction mixture was diluted with water (250 mL) and then extracted with chloroform (3 x 100 mL). The extracts were combined and concentrated under reduced pressure. The residue was purified by HPFC eluting with a gradient of 0 – 20% CMA in chloroform over 700 mL and then with 20% CMA in chloroform over 400 mL. The resulting solid was recrystallized from 100:1 acetonitrile:water to provide 6 mg of 4-{{(4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]methyl}-*N*-[2-(1*H*-indol-2-yl)ethyl]benzenesulfonamide as an off-white solid, mp 100.0-101.0 °C. MS (APCI) *m/z* 558 (M + H)⁺; Anal. calcd for C₂₉H₂₇N₅O₃S₂: C, 62.46; H, 4.88; N, 12.56. Found C, 62.27; H, 4.63; N, 12.73.

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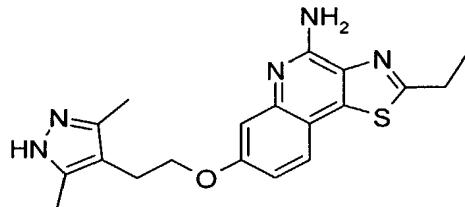
Example 38

7-[(6-Chloropyridin-2-yl)methoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine

5 A mixture of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (245 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), and DMF (15 mL) was stirred at 75 °C for 10 minutes. 2-Chloro-5-(chloromethyl)pyridine (178 mg, 1.1 mmol) was added in portions over a period of 30 minutes. The reaction mixture was stirred for 1 hour and then the heat source was
10 removed. The reaction mixture was diluted with water (200 mL) and then filtered. The isolated solid was rinsed with water and then dried to provide an off white powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0 - 15 % CMA in chloroform 700 mL and then with 15 % CMA in chloroform over 600 mL. The resulting solid was slurried with hot 10:1 acetonitrile:methanol to
15 provide 216 mg of 7-[(6-chloropyridin-2-yl)methoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as a pale yellow solid, mp 229.0-230.0 °C. MS (APCI) *m/z* 371 (M + H)⁺; Anal. calcd for C₁₈H₁₅ClN₄OS•0.1 CHCl₃: C, 57.06; H, 4.32; N, 14.63. Found C, 56.79; H, 3.98; N, 14.63.

20

Example 39

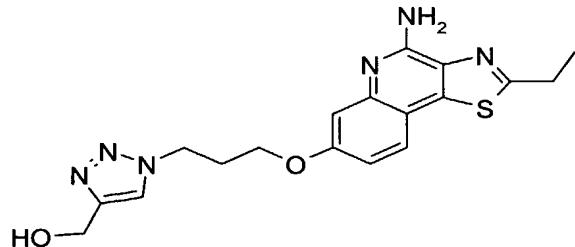
7-[2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine

A mixture of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (245 mg, 1.0 mmol), cesium carbonate (1.3 g, 4.0 mmol), and DMF (20 mL) was stirred at 75 °C for 10 minutes. 4-(Bromoethyl)-3,5-dimethyl-1*H*-pyrazole (223 mg, 1.1 mmol) was added in portions over a period of 30 minutes. The reaction mixture was stirred for 20 minutes and then the heat source was removed. The reaction mixture was diluted with water (250 mL), stirred overnight, and then filtered. The isolated solid was rinsed with water and then dried to provide a tan powder. This material was dissolved in dichloromethane and then purified by HPFC eluting with a gradient of 0- 30 % CMA in chloroform 700 mL and then with 30 % CMA in chloroform over 200 mL. The resulting solid was recrystallized from 5 50:1 acetonitrile:methanol (40 mL) to provide 205 mg of 7-[2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as an off white solid, mp 195.0-197.0 °C. MS (APCI) *m/z* 368 (M + H)⁺; Anal. calcd for C₁₉H₂₁N₅OS: C, 62.10; H, 5.764; N, 10 19.06. Found C, 61.95; H, 5.53; N, 19.09.

15

Example 40

(1-{{[3-(4-Amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]propyl}-
1*H*-[1,2,3]triazol-4-yl)methanol



20

Part A

A mixture of 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (1.00 mg, 4.08 mmol), cesium carbonate (5.30 g, 16.3 mmol), and DMF (40 mL) was stirred at 50 °C for 10 minutes. A portion (0.05 mL) of a solution (1.1 mL) of 1-bromo-3-chloropropane (705 mg, 4.48 mmol) in DMF was added every 7 minutes. After 2 hours the reaction mixture 25 was poured into water (225 mL). The mixture was stirred for 30 minutes and then filtered. The isolated solid was dried to provide 785 mg of 7-(3-chloropropoxy)-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as a brown solid.

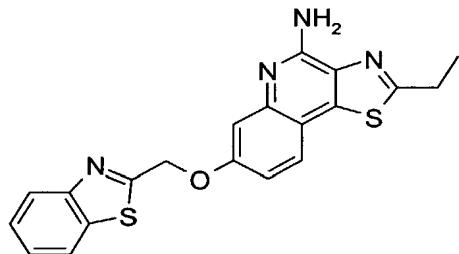
Part B

A solution of 7-(3-chloropropoxy)-2-ethylthiazolo[4,5-*c*]quinolin-4-amine (684 mg, 2.12 mmol) in DMF (20 mL) was heated to 110 °C. Sodium azide (151 mg, 2.33 mol) was added in a single portion. After 1 hour the reaction mixture was poured into water (100 mL). The mixture was extracted with chloroform (3 x 100 mL). The combined extracts were concentrated under reduced pressure. The residue was dissolved in chloroform and purified by HPFC eluting with a gradient of 0 – 20% CMA in chloroform over 700 mL and then with 20 % CMA in chloroform over 600 mL to provide 400 mg of 7-(3-azidopropoxy)-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as a pale yellow solid.

Part C

The material from Part B (1.21 mmol), propargyl alcohol (134 mg, 2.4 mmol), copper(II) sulfate pentahydrate (30 mg, 0.12 mmol), sodium ascorbate (24 mg, 0.12 mmol), water (2 mL), and DMF (8 mL) were combined and stirred at 70 °C for 2 hours. The reaction mixture was cooled, diluted with water (200 mL), stirred for 40 minutes, and then filtered. The isolated solid was dissolved in chloroform and purified by HPFC eluting with a gradient of 0 – 30 % CMA in chloroform over 700 mL and then with 30% CMA in chloroform over 600 mL. The resulting solid was slurried with hot 10:1 acetonitrile:methanol to provide 280 mg of (1-{[3-(4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]propyl}-1*H*-[1,2,3]triazol-4-yl)methanol as an off white solid, mp 194.0-197.0 °C. MS (APCI) *m/z* 385 (M + H)⁺; Anal. calcd for C₁₈H₂₀N₆O₂S: C, 56.23; H, 5.24; N, 21.86. Found C, 56.49; H, 5.12; N, 21.94.

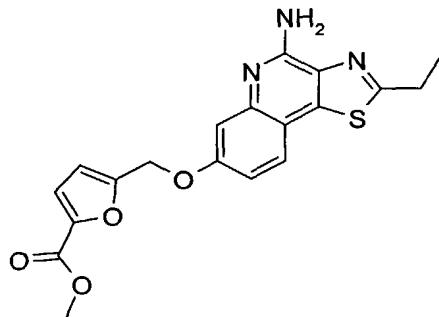
Example 41

25 7-[(1,3-Benzothiazol-2-yl)methoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine

A scintillation vial was charged with 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol and anhydrous *N,N*-dimethylformamide (DMF, 2 mL). The mixture was warmed until a solution was obtained. An additional amount of DMF (1 mL) was added. To this stirred orange solution was added cesium carbonate (3.0 eq.) and a solution of 2-
5 (bromomethyl)benzothiazole dissolved in DMF (2 mL). Additional DMF (1 mL) was used to rinse the vial. The vial was capped and heated to 60 °C overnight. The reaction was monitored by HPLC. The reaction was quenched by adding the reaction mixture dropwise to water (60 mL) with stirring. A precipitate formed. The solid was collected by vacuum filtration. The solid was then dissolved in methanol and adsorbed onto silica gel
10 (6 g) for purification by HPFC (0-15% CMA in chloroform, 1440 mL). Pure fractions were combined and concentrated; the resulting solid was recrystallized from acetonitrile to provide 7-[(1,3-benzothiazol-2-yl)methoxy]-2-ethylthiazolo[4,5-*c*]quinolin-4-amine as a white crystalline solid, mp. 211-212 °C. MS (APCI) *m/z* 393 (M+H)⁺. Anal. calcd C₂₀H₁₆N₄OS₂ • 0.6 H₂O: C, 59.56; H, 4.30; N, 13.89. Found: C, 59.66; H, 4.08; N, 13.80.
15

Example 42

Methyl 5-{{(4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy}methyl}-2-furoate

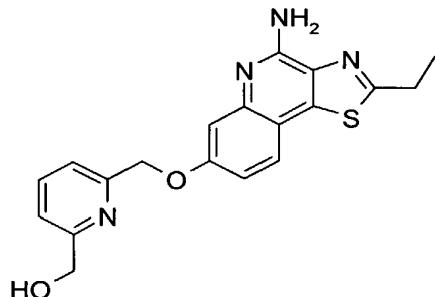


20 A scintillation vial was charged with 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (1.0 eq., 1.0 mmol) and anhydrous DMF (2 mL). The mixture was warmed until a solution was obtained. An additional amount of DMF (1 mL) was added. To this stirred orange solution was added cesium carbonate (3.0 eq., 3.0 mmol) and a solution of ethyl 5-(chloromethyl)-2-furancarboxylate (1.0 eq., 1.0 mmol) dissolved in DMF (2 mL).
25 Additional DMF (1 mL) was used to rinse the vial. The vial was capped and heated to 60 °C overnight. The reaction was monitored by HPLC. The reaction was quenched by

adding the reaction mixture drop-wise to water (60 mL) with stirring. A precipitate formed. Crude ethyl 5-{{(4-amino-2-ethylthiazolo[4,5-c]quinolin-7-yl)oxy}methyl}-2-furoate was isolated as a solid by vacuum filtration. The solid was then dissolved in methanol and adsorbed onto silica gel (6 g) for purification by HPFC (0-15% CMA in chloroform, 1440 mL). Pure fractions were combined and concentrated to provide a solid which analysis indicated was the methyl ester. This material was recrystallized from acetonitrile to provide methyl 5-{{(4-amino-2-ethylthiazolo[4,5-c]quinolin-7-yl)oxy}methyl}-2-furoate as a light yellow crystalline solid, mp 184-186 °C. MS (APCI) *m/z* 384 (M+H)⁺. Anal. calcd for C₁₉H₁₇N₃O₄S • 0.30 CH₃CN: C, 59.49; H, 4.56; N, 11.68. Found: C, 59.35; H, 4.22; N, 11.71.

Example 43

6-{{(4-Amino-2-ethylthiazolo[4,5-c]quinolin-7-yl)oxy}methyl}pyridin-2-yl)methanol



15

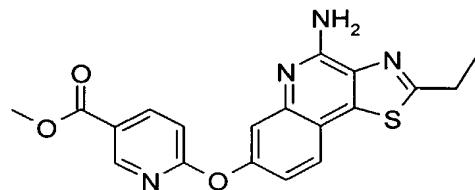
A scintillation vial was charged with 4-amino-2-ethylthiazolo[4,5-c]quinolin-7-ol (1.0 eq., 1.0 mmol) and anhydrous DMF (2 mL). The mixture was warmed until a solution was obtained. An additional amount of DMF (1 mL) was added. To this stirred orange solution was added cesium carbonate (3.0 eq., 3.0 mmol) and a solution of 6-(bromomethyl)-2-pyridinemethanol (1.0 eq., 1.0 mmol) dissolved in DMF (2 mL). Additional DMF (1 mL) was used to rinse the vial. The vial was capped and heated to 60 °C overnight. The reaction was monitored by HPLC. The reaction was quenched by adding the reaction mixture drop-wise to water (60 mL) with stirring. A precipitate formed. The solid was collected by vacuum filtration. The solid was then dissolved in methanol and adsorbed onto silica gel (6 g) for purification by HPFC (0-15% CMA-chloroform, 1440 mL). Pure fractions were combined and concentrated; the resulting solid was recrystallized from acetonitrile to provide 6-{{(4-amino-2-ethylthiazolo[4,5-

c]quinolin-7-yl)oxy]methyl}pyridin-2-yl)methanol as a pale yellow crystalline solid, mp 186-187 °C. MS (APCI) *m/z* 367 (M+H)⁺. Anal. calcd for C₁₉H₁₈N₄O₂S • 0.30 H₂O: C, 61.37; H, 5.04; N, 15.07. Found: C, 61.08; H, 4.92; N, 15.11.

5

Example 44

Methyl 6-[(4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]nicotinate

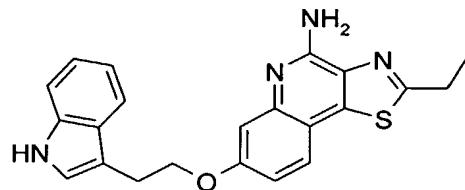


A round bottom flask was charged with 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (1.0 eq., 2.0 mmol), methyl 6-chloronicotinate (1.0 eq., 2.0 mmol), cesium carbonate (3.0 eq. 6.0 mmol), and anhydrous 1,4-dioxane (45 mL). The mixture was heated to reflux for 24 hours. The reaction was monitored by HPLC. The reaction mixture was concentrated to dryness. The resulting solid was then dissolved in methanol and adsorbed onto silica gel (6 g) for purification by HPFC (0-15% CMA in chloroform, 1440 mL).
 10 Pure fractions were combined and concentrated; the resulting solid was recrystallized from acetonitrile to provide methyl 6-[(4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-yl)oxy]nicotinate as a light peach colored crystalline solid, mp 213-214 °C. MS (APCI) *m/z* 381 (M+H)⁺. Anal. calcd for C₁₉H₁₆N₄O₃S: C, 59.99; H, 4.24; N, 14.73. Found: C, 59.76; H, 4.19; N, 14.71.
 15

20

Example 45

2-ethyl-7-[2-(1*H*-indol-3-yl)ethoxy]thiazolo[4,5-*c*]quinolin-4-amine

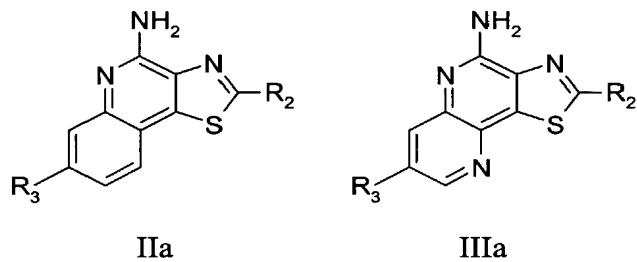


A scintillation vial was charged with 4-amino-2-ethylthiazolo[4,5-*c*]quinolin-7-ol (1.0 eq., 1.0 mmol) and anhydrous DMF (2 mL). The mixture was warmed until a

solution was obtained. An additional amount of DMF (1 mL) was added. To this stirred orange solution was added cesium carbonate (3.0 eq., 3.0 mmol) and a solution of 3-(2-bromoethyl)indole (1.0 eq., 1.0 mmol) dissolved in DMF (2 mL). Additional DMF (1 mL) was used to rinse the vial. The vial was capped and heated to 60 °C overnight. The 5 reaction was monitored by HPLC. The reaction was quenched by adding the reaction mixture drop-wise to water (60 ml) with stirring. A precipitate formed. The solid was collected by vacuum filtration. The solid was then dissolved in methanol and adsorbed onto silica gel (6 g) for purification by HPFC (0-15% CMA in chloroform, 1440 mL). Pure fractions were combined and concentrated; the resulting solid was recrystallized from 10 methanol to provide a peach colored crystalline solid, mp 218-220 °C. MS (APCI) *m/z* 389 (M+H)⁺. Anal. calcd for C₂₂H₂₀N₄OS • 0.8 CH₃OH: C, 66.13; H, 5.65; N, 13.53. Found: C, 66.43; H, 5.03; N, 13.90.

Exemplary Compounds

15 Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIa or IIIa) and the following R₂ and R_{3a} substituents, wherein each line of the table is matched with Formula IIa or IIIa to represent a specific compound.



| R ₂ | R ₃ |
|----------------|------------------------|
| methyl | 4-fluorobenzoyloxy |
| methyl | 2,4-difluorobenzoyloxy |
| methyl | 6-chlorobenzoyloxy |
| methyl | 2-chlorobenzoyloxy |
| methyl | (pyridin-3-yl)methoxy |

| R ₂ | R ₃ |
|----------------|--------------------------|
| methyl | (pyridin-4-yl)methoxy |
| methyl | 2-(4-fluorophenyl)ethoxy |
| ethyl | 4-fluorobenzylloxy |
| ethyl | 2,4-difluorobenzylloxy |
| ethyl | 6-chlorobenzylloxy |
| ethyl | 2-chlorobenzylloxy |
| ethyl | (pyridin-3-yl)methoxy |
| ethyl | (pyridin-4-yl)methoxy |
| ethyl | 2-(4-fluorophenyl)ethoxy |
| propyl | 4-fluorobenzylloxy |
| propyl | 2,4-difluorobenzylloxy |
| propyl | 6-chlorobenzylloxy |
| propyl | 2-chlorobenzylloxy |
| propyl | (pyridin-3-yl)methoxy |
| propyl | (pyridin-4-yl)methoxy |
| propyl | 2-(4-fluorophenyl)ethoxy |
| methoxymethyl | 4-fluorobenzylloxy |
| methoxymethyl | 2,4-difluorobenzylloxy |
| methoxymethyl | 6-chlorobenzylloxy |
| methoxymethyl | 2-chlorobenzylloxy |
| methoxymethyl | (pyridin-3-yl)methoxy |
| methoxymethyl | (pyridin-4-yl)methoxy |
| methoxymethyl | 2-(4-fluorophenyl)ethoxy |
| ethoxymethyl | 4-fluorobenzylloxy |
| ethoxymethyl | 2,4-difluorobenzylloxy |
| ethoxymethyl | 6-chlorobenzylloxy |
| ethoxymethyl | 2-chlorobenzylloxy |
| ethoxymethyl | (pyridin-3-yl)methoxy |
| ethoxymethyl | (pyridin-4-yl)methoxy |
| ethoxymethyl | 2-(4-fluorophenyl)ethoxy |

| R ₂ | R ₃ |
|----------------|--------------------------|
| 2-methoxyethyl | 4-fluorobenzylxy |
| 2-methoxyethyl | 2,4-difluorobenzylxy |
| 2-methoxyethyl | 6-chlorobenzylxy |
| 2-methoxyethyl | 2-chlorobenzylxy |
| 2-methoxyethyl | (pyridin-3-yl)methoxy |
| 2-methoxyethyl | (pyridin-4-yl)methoxy |
| 2-methoxyethyl | 2-(4-fluorophenyl)ethoxy |

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to modulate cytokine biosynthesis by 5 inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity 10 is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN- α and TNF- α , respectively) secreted into culture media as described by Testerman et. al. in “Cytokine Induction by the Immunomodulators Imiquimod and S-27609”, *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

15 Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered 20 Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI

complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

5 The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

10

Incubation

The solution of test compound is added at 60 μ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the 15 desired range (usually 30-0.014 μ M). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37 °C in a 5% carbon dioxide atmosphere.

Separation

20 Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4 °C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN- α by ELISA and for TNF- α by IGEN/BioVeris Assay.

25

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN- α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

30

The TNF- α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF- α capture and

detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

5 In total, the data output of the assay consists of concentration values of TNF- α and IFN- α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. If any negative values result from
10 background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound
15 based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61
20 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

30 The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using 5 HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC 10 suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μ M. Controls include cell 15 samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in 20 DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μ M) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension 25 bringing the test compound concentrations to the desired range (usually 30 - 0.014 μ M) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37 °C in a 5% carbon dioxide atmosphere.

30 Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4 °C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates

are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70 °C until analysis.

5

Interferon- α and Tumor Necrosis Factor- α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF- α and human IFN- α that have been pre-coated on specific spots. Each well contains four spots: one human TNF- α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF- α capture and detection antibody pair is from MesoScale Discovery. The human IFN- α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN- α subtypes except IFN- α F (IFNA21). Standards consist of recombinant human TNF- α (R&D Systems, Minneapolis, MN) and IFN- α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN- α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN- α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

20

15

Assay Data and Analysis

25

In total, the data output of the assay consists of concentration values of TNF- α or IFN- α (y-axis) as a function of compound concentration (x-axis).

30

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to

calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates.

5 Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN- α , TNF- α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 10 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

15 A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the 20 sum of the median dose values from an average of previous experiments.

25 The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

TNF- α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF- α) when tested using the method described below.

5 The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor- α (TNF- α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

10 Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3×10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 μ L) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3×10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

15 Compound Preparation

20 The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by a dose response assay.

25 Incubation

20 A solution of test compound (1 μ l) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μ L, EC₇₀ concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF- α Analysis

Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon

5 LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4×10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μ L) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1×10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

15

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μ l) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μ L, EC₇₀ concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

30 TNF- α Analysis

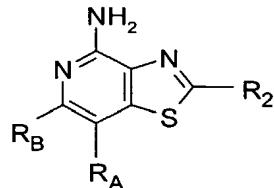
Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon LPS stimulation alone is considered a 100% response.

5 The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited
10 by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



I

wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R₃ group, or substituted by one R₃ group and one R group;

10 R₂ is selected from the group consisting of:

- hydrogen,
- alkyl,
- hydroxyalkylenyl,
- haloalkylenyl,
- 15 alkenyl,
- alkyl-O-alkylenyl,
- alkyl-O-alkenylenyl,
- alkenyl-O-alkylenyl,
- alkenyl-O-alkenylenyl,
- 20 N(R₈)₂-alkylenyl,
- N₃-alkylenyl,
- N(R₈)₂-C(O)-O-alkylenyl,
- heterocyclyl,
- heterocyclyl-O-alkylenyl,
- 25 heterocyclyl-O-alkenylenyl,
- aryl,
- aryl-O-alkylenyl,
- aryl-O-alkenylenyl,
- heteroaryl,

heteroaryl-O-alkylenyl, and
heteroaryl-O-alkenylényl;

R₃ is selected from the group consisting of:

-O-Z-Ar,
5 -O-Z-Ar'-Y-R₄,
-O-Z-Ar'-X-Y-R₄,
-O-Z-Ar'-R₅, and
-O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and
10 alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with
-O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can
be unsubstituted or can be substituted by one or more substituents independently selected
from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,
15 haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,
aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy,
heterocyclyl, heterocyclylalkylene, amino, alkylamino, and dialkylamino;

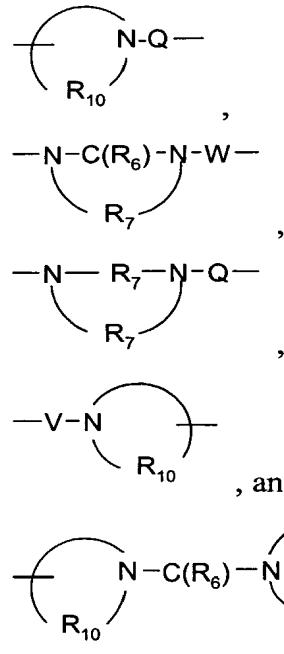
Ar' is selected from the group consisting of arylene and heteroarylene both of
which can be unsubstituted or can be substituted by one or more substituents
20 independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl,
haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,
aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy,
heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene,
25 arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and
alkynylene groups can be optionally interrupted by arylene, heteroarylene or
heterocyclylene or by one or more -O- groups.

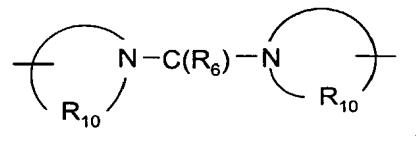
Y is selected from the group consisting of:

-S(O)₀₋₂-,
30 -S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-O-,

-O-C(R₆)-,
- $O-C(O)-O-$,
-N(R₈)-Q-,
-C(R₆)-N(R₈)-,
5 -O-C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-,



10

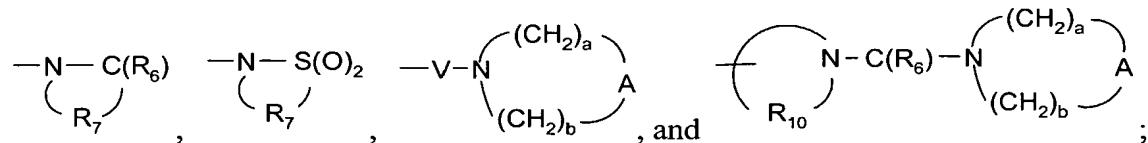


15

20

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

5 R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and 10 -N(R₄)-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

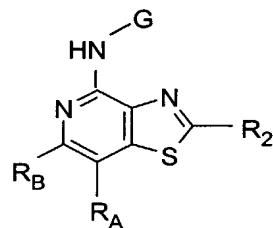
15 W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

and

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

20 or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (VII):



VII

25 wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one R_3 group, or substituted by one R_3 group and one R group;

R_2 is selected from the group consisting of:

| | |
|----|---|
| 5 | hydrogen, alkyl, hydroxyalkylenyl, haloalkylenyl, alkenyl, |
| 10 | alkyl-O-alkylenyl, alkyl-O-alkenylenyl, alkenyl-O-alkylenyl, alkenyl-O-alkenylenyl, N(R ₈) ₂ -alkylenyl, |
| 15 | N ₃ -alkylenyl, N(R ₈) ₂ -C(O)-O-alkylenyl, heterocyclyl, heterocyclyl-O-alkylenyl, heterocyclyl-O-alkenylenyl, |
| 20 | aryl, aryl-O-alkylenyl, aryl-O-alkenylenyl, heteroaryl, heteroaryl-O-alkylenyl, and |
| 25 | heteroaryl-O-alkenylenyl; |

R_3 is selected from the group consisting of:

30 -O-Z-Ar,
 -O-Z-Ar'-Y-R₄,
 -O-Z-Ar'-X-Y-R₄,
 -O-Z-Ar'-R₅, and
 -O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-;

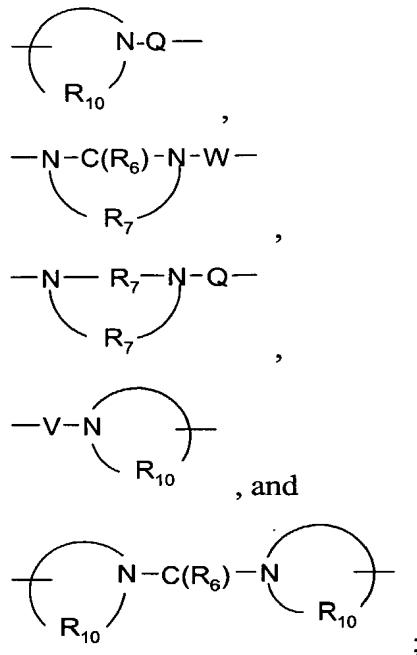
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylene, amino, alkylamino, and dialkylamino;

10 Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclene or by one or more -O- groups.

20 Y is selected from the group consisting of:

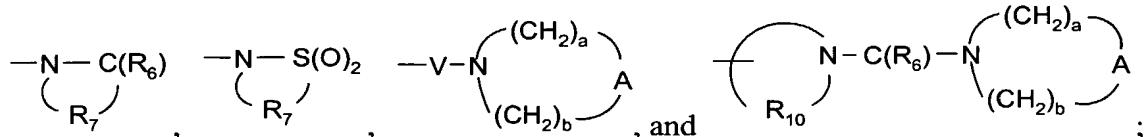
- S(O)₀₋₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-O-,
- O-C(R₆)-,
- O-C(O)-O-,
- N(R₈)-Q-,
- C(R₆)-N(R₈)-,
- O-C(R₆)-N(R₈)-,
- C(R₆)-N(OR₉)-,



5

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



20

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

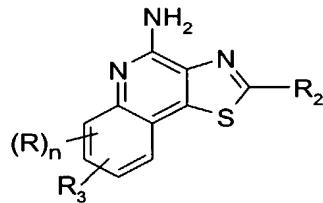
R₉ is selected from the group consisting of hydrogen and alkyl;
 R₁₀ is C₃₋₈ alkylene;
 A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;
 5 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;
 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,
 10 W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-,
 a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7 ;
 R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;
 G is selected from the group consisting of:
 15 -C(O)-R',
 α -aminoacyl,
 α -aminoacyl- α -aminoacyl,
 -C(O)-O-R',
 -C(O)-N(R")R',
 -C(=NY')-R',
 20 -CH(OH)-C(O)-OY',
 -CH(OC₁₋₄ alkyl)Y₀,
 -CH₂Y₁, and
 -CH(CH₃)Y₁;
 R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl,
 25 C₃₋₇ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylene, heteroarylC₁₋₄ alkylene, haloC₁₋₄ alkylene, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also
 30 be hydrogen;
 α -aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl;

Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl, mono-*N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl, and di-*N,N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl;

5 Y₁ is selected from the group consisting of mono-*N*-C₁₋₆ alkylamino, di-*N,N*-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl;
or a pharmaceutically acceptable salt thereof.

10 3. A compound of formula (II):



II

wherein:

15 R₂ is selected from the group consisting of:

- hydrogen,
- alkyl,
- hydroxyalkylenyl,
- haloalkylenyl,
- alkenyl,
- alkyl-O-alkylenyl,
- alkyl-O-alkenyl,
- alkenyl-O-alkylenyl,
- alkenyl-O-alkenyl,

20
25 N(R₈)₂-alkylenyl,
N₃-alkylenyl,
N(R₈)₂-C(O)-O-alkylenyl,
heterocyclyl,
heterocyclyl-O-alkylenyl,

heterocycl-O-alkenyl, 5

aryl,

aryl-O-alkylenyl,

aryl-O-alkenyl, 10

heteroaryl,

heteroaryl-O-alkylenyl, and

heteroaryl-O-alkenyl;

R_3 is selected from the group consisting of:

-O-Z-Ar,

10 -O-Z-Ar'-Y-R₄,

-O-Z-Ar'-X-Y-R₄,

-O-Z-Ar'-R₅, and

-O-Z-Ar'-X-R₅;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and 15 alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, 20 haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocycl, heterocyclalkylene, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents 25 independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocycl, heterocyclalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, 30 arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclene or by one or more -O- groups.

Y is selected from the group consisting of:

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

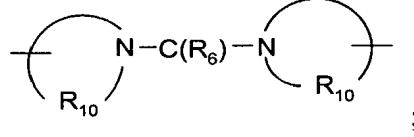
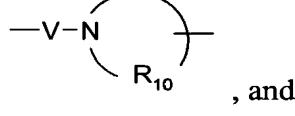
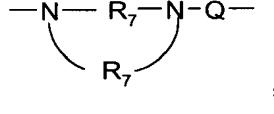
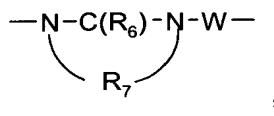
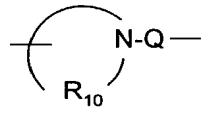
-O-C(O)-O-,

-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

-C(R₆)-N(OR₉)-,



R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

20 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

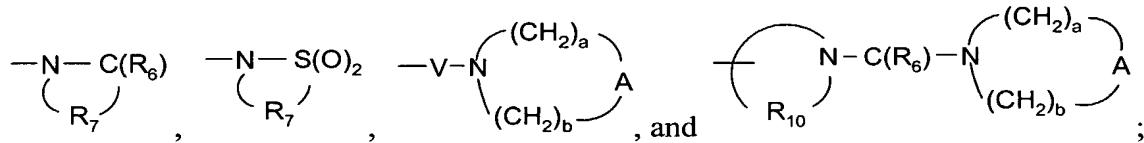
can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,

nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

10 R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

15 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-,

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7 ;

20 R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

25 4. The compound or salt of claim 3 wherein R₃ is attached at the 7-position.

5. The compound or salt of claim 3 wherein n is 0.

6. The compound or salt of any one of claims 1 through 5 wherein Z is a bond, 30 alkylene, or alkylene interrupted with one -O-.

7. The compound or salt of claim 6 wherein Z is -C₁₋₃ alkylene-.

8. The compound or salt of claim 7 wherein Z is -CH₂-.

5

9. The compound or salt of any one of claims 1 through 8 wherein R₃ is -O-Z-Ar.

10. The compound or salt of any one of claims 1 through 9 wherein Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, 1,2,3-triazolyl, indolyl, benzothiazolyl, and oxazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, trifluoromethoxy, aryl, and hydroxyalkyl.

15 11. The compound or salt of claim 10 wherein Ar is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrrolyl, thienyl, furyl, isoxazolyl, thiazolyl, and imidazolyl; each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, and trifluoromethoxy.

20

12. The compound or salt of claim 11 wherein Ar is phenyl substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, nitro, cyano, halogen, amino, alkylamino, dialkylamino, and trifluoromethoxy.

25 13. The compound or salt of any one of claims 1 through 8 wherein R₃ is -O-Z-Ar'-Y-R₄.

30 14. The compound or salt of claim 13 wherein:
Ar' is phenylene, naphthylene, pyridylene, pyrrolylene, thienylene, or furylene;
Y is selected from the group consisting of:

-S(O)₀₋₂,

-S(O)₂-N(R₈)-,

-C(O)-,
-N(R₈)-C(O)-,
-N(R₈)-S(O)₂-, and
-N(R₈)-C(R₆)-N(R₈)-;

5 wherein:

R₈ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and
alkoxyalkylenyl; and

R₄ is selected from the group consisting of alkyl, aryl, heteroaryl,
heteroarylalkylenyl, and heterocyclyl.

10

15. The compound or salt of any one of claims 1 through 8, 13, or 14 wherein Ar' is
phenylene.

15

16. The compound or salt of any one of claims 1 through 15 wherein R₂ is selected
from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ alkyl-O-C₁₋₈ alkyl.

20

17. The compound or salt of claim 16 wherein R₂ is hydrogen, C₁₋₄ alkyl, or
C₁₋₄ alkyl-O-C₁₋₄ alkyl.

25

18. The compound or salt of claim 17 wherein R₂ is methyl, ethyl, n-propyl, n-butyl,
2-methoxyethyl, methoxymethyl, or ethoxymethyl.

19. A pharmaceutical composition comprising a therapeutically effective amount of a
compound or salt of any one of claims 1 through 18 and a pharmaceutically acceptable
carrier.

30

20. A method of inducing cytokine biosynthesis in an animal comprising administering
an effective amount of a compound or salt of any one of claims 1 through 18 or a
pharmaceutical composition of claim 19 to the animal.

21. A method of treating a viral disease in an animal in need thereof comprising administering an effective amount of a compound or salt of any one of claims 1 through 18 or a pharmaceutical composition of claim 19 to the animal.
- 5 22. A method of treating a neoplastic disease in an animal in need thereof comprising administering an effective amount of a compound or salt of any one of claims 1 through 18 or a pharmaceutical composition of claim 19 to the animal.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/21426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/4365, 31/438; C07D 513/04, 513/14
US CL : 546/83, 84; 514/293

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/83, 84; 514/293

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN structure, File Registry, File Caplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 03/080114 A2 (POWDERJECT RESEARCH LIMITED) 02 October 2003 (02.10.2003). | 1-22 |
| X | WO 03/045391 A1 (3M INNOVATIVE PROPERTIES COMPANY) 05 June 2003 (05.06.2003), entire document. | 1-22 |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent published on or after the international filing date

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&" document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

28 October 2005 (28.10.2005)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
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Date of mailing of the international search report

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